

## **MEETING SUMMARY**

### **The U.S. Environmental Protection Agency Meeting on Pharmaceuticals in the Environment**

**U.S. Environmental Protection Agency  
National Exposure Research Laboratory  
Executive Building, Auditorium  
Las Vegas, NV**

**August 23-25, 2005**

#### **SUMMARY OF IDEAS AND PERSPECTIVES**

The Meeting on Pharmaceuticals in the Environment, organized by a cross-Agency planning group within the U.S. Environmental Protection Agency (EPA), was the first meeting to bring together the many diverse stakeholders and federal agencies that have a role in minimizing the occurrence of pharmaceuticals and personal care products (PPCPs) in waste streams, as well as those scientists who are evaluating the occurrence, fate, and effects of these compounds in the environment. All participants seemed very appreciative of the opportunity to talk across communities and hear the perspectives and issues from others' points of view. Some highlights from the meeting discussions include the following items:

- Many participants expressed the perspective that the information to date does not indicate an impact to human health. Clear evidence that PPCPs are in the environment and, in some cases, may be ubiquitous coupled with findings of reproductive effects to aquatic life, indicate a need for further research.
- Additional research is needed on the fate and effects of pharmaceuticals and their transformation products at levels detected in the environment.
- It was proposed that the federal government assist in targeting future research efforts toward areas of greatest risk by developing a priority list of PPCPs that occur and most likely are to have human health or ecological effects.
- It also was suggested that existing detection methods be validated and additional method development research be conducted (i.e., methods that can detect multiple PPCPs in different media types, such as sediments and water, including sample preparation and concentration approaches).

There is much interest and activity in proper drug disposal so that unused pharmaceuticals do not enter the solid waste or wastewater streams. Unused pharmaceuticals are those that currently are disposed of because they are past their expiration date or no longer needed.

It was observed that federal involvement from many agencies might be needed to facilitate these efforts. Those federal agencies that could become involved include: EPA, the Centers for Disease Control and Prevention (CDC), the Drug Enforcement Administration (DEA), the U.S. Food and Drug Administration (FDA), the National Institute of Environmental Health Sciences, the National Oceanic and Atmospheric Administration (NOAA), the U.S. Geological Survey (USGS), and the U.S. Department of Agriculture (USDA).

It also was recognized that there is a large stakeholder community that could contribute to these efforts. Among these are the healthcare community, medical societies, the medical insurance industry, the veterinary profession, pharmaceutical manufacturers, pharmacies, approved pharmaceutical “reverse distributors”, state and local governments, and wastewater treatment plant (WWTP) operators.

There was discussion of the interest of local and state governments to conduct take-back programs in an attempt to reduce pharmaceutical waste. Some participants proposed that efforts be made to remove barriers to these types of programs and encourage this pollution prevention approach.

Meeting participants posed the question of if there is a need for a new approach to address the issue of emerging contaminants such as PPCPs. It was proposed that such an approach could focus on collaboration with stakeholders to understand the issue and find the best solutions.

## **INTRODUCTION AND OVERVIEW**

The EPA Meeting on Pharmaceuticals in the Environment was held on August 23-25, 2005, in Las Vegas, Nevada. The workshop brought together researchers from academia, private industry, regulatory agencies, and government to discuss ongoing research on pharmaceuticals in the environment. The workshop also served as a stimulus for increased collaborations among the various researchers and agencies and resulted in improved knowledge of pharmaceuticals in the environment. Approximately 160 individuals attended.

### ***Welcome and Introductory Remarks***

**Christian Daughton, U.S. EPA**

Dr. Daughton welcomed participants to the meeting and explained that there were two distinct but interrelated objectives of the meeting: (1) provide a forum for the National Center for Environmental Research’s (NCER) Science To Achieve Results (STAR) extramural grant program grantees to present their results on PPCPs; and (2) focus on environmental stewardship for pharmaceuticals. This topic had never been discussed at a public meeting in a concerted fashion, and the meeting brought together a broad audience of scientists, engineers, health care professionals, and regulatory and enforcement professionals. The attendees were employed by a variety of organizations, including federal, state, and local agencies; public utilities; universities; consulting firms; private laboratories; pharmaceutical manufacturers; and health care and medical facilities. He gave an overview of the format and rules of the meeting, thanked the planning committee, and introduced Angela Page of EPA as the next speaker.

### ***Overview of the Office of Research and Development and Science To Achieve Results Program***

**Angela Page, U.S. EPA**

Ms. Page welcomed participants to the meeting and thanked the STAR grantees for agreeing to share their results in this forum. She explained that the Office of Research and Development (ORD) is tasked with providing credible, relevant, and timely research results and technical support to inform EPA policy decisions. ORD is organized into 3 national laboratories, 4 national centers, and 2 offices located in 14 facilities around the country and in Washington, DC, and employs more than 1,950 personnel. In 2002, ORD established the National Homeland Security Research Center and established the National Center for Computational Toxicology in 2004. In line with the National Academy of Sciences’ risk assessment and risk management paradigm, the three national laboratories focus on exposure research in the following high-priority research areas: human health, particulate matter, drinking water, clean water, global change, endocrine disruptors, ecological risk, pollution prevention, and homeland security.

NCER, ORD’s extramural research arm, was established in 1995 as part of the ORD reorganization. NCER, through its STAR grants program, awards competitive grants to leading researchers from the ac-

ademic and nonprofit communities. NCER awards small contracts to for-profit organizations under the Small Business Innovation Research Program. In addition, NCER also establishes both STAR and non-STAR research centers, such as the Hazardous Substance Research Centers. Using the ORD Strategic Plan, national environmental research needs, relevance to Agency mission, and research conducted in ORD's intramural program, ORD cooperates with other EPA offices, including Regional Offices, to select topics for STAR solicitations. Each year, approximately 2,000 to 2,500 grant applications are received in response to 20 to 25 requests for applications; 100 to 175 research grants and 125 to 150 fellowships are awarded annually.

NCER's Drinking Water Program began in 1996 with funding levels between \$2.5 and \$5 million per year. Over the course of the Drinking Water Research Program, research has been funded to investigate exposure and health impacts of microorganisms such as *Cryptosporidium*; exposure and risk from disinfection byproducts; effects and occurrence of chemicals on or anticipated to be included on the Contaminant Candidate List (CCL), including PPCPs; and epidemiological studies to study microbial risk. NCER activities are communicated via online access and resources, publications, progress review workshops and proceedings, scientific conferences, and the NCER Web Site at <http://www.epa.gov/ncer>.

***Overview Presentation From the U.S. EPA's Office of Water***  
**Octavia Conerly, U.S. EPA**

The Health and Ecological Criteria Division of EPA's Office of Water (OW) provides the science behind EPA regulations for water. EPA's enabling legislation can be a very diverse set of laws, not always consistent with one another, that often require science-based decisions (e.g., the Safe Drinking Water Act [SDWA] of 1996 requires EPA to use the best publicly available, peer-reviewed science) and dictate how EPA does business. The major legislative authorities for water include the SDWA; the Clean Water Act (CWA) of 1977; and the Food Quality Protection Act (FQPA) of 1996, which provides a safety standard for all pesticides used on food.

EPA does not have a specific program targeting the regulation of PPCPs. Therefore, regulatory determinations for PPCPs are currently handled under one of EPA's existing programs. One such program is the Contaminant Candidate List(ing) (CCL) process. Under the SDWA, OW is mandated to set maximum levels for contaminants in water delivered to users of public water systems with an emphasis on the best available peer-reviewed science and the protection of sensitive populations. EPA is required to regulate at least five contaminants every 5 years via the CCL.

Under the SDWA, for a contaminant to be regulated, three criteria must be met. The three criteria are: (1) The contaminant must adversely affect public health. (2) The contaminant must be known to occur or likely to occur in public water systems with a frequency and at levels posing a threat to public health. (3) There must be present a meaningful opportunity for health risk reduction if regulation occurs. Every 6 years, EPA reviews existing National Primary Drinking Water Standards for drinking water contaminants. Currently, there are no existing regulations for specific PPCPs. Some PPCPs, however, are pesticides (e.g., nonylphenol) or endocrine disruptors. In such cases, these compounds may be regulated within these specific programs.

Presently, there are significant data gaps (e.g., analytical methods, health effects data, national occurrence data) for PPCPs that limit their ability to be regulated at this time. Another limitation is the fact that under SDWA and CWA, OW cannot request toxicological data from manufacturers or industry.

The CWA allows EPA to set water quality criteria and standards, as well as technology-based standards for ambient waters to protect and restore U.S. waters. States and tribes set their own water quality standards with EPA guidance. If the proposed standards are not as protective and/or as scientifically

sound as EPA's criteria, EPA may reject them. EPA publishes national chemical and biological water quality criteria based on risk assessments, allowing states to designate appropriate use for their water bodies. With the exception of nonylphenol (used as a pesticide and a surfactant), the Agency has not yet developed criteria for PPCPs as toxics but could if adequate supporting data are available.

Other CWA approaches that could help control the levels of PPCPs in ambient waters include the Effluent Guidelines program for the regulation of point sources (e.g., the pharmaceutical manufacturing industry and the aquaculture industry), the Combined Animal Feeding Operations (CAFO) Rule, and the Fish Advisory Program. In general, effluent guidelines are national standards for wastewater discharges to surface waters and publicly owned treatment works (POTW), such as municipal sewage treatment plants (STPs). The guidelines are based on the performance of treatment and control technologies and not on risk or impacts upon receiving waters. The Effluent Guidelines for the Pharmaceutical Manufacturing Industry Rule regulates the discharge of pollutants related to the manufacture of pharmaceuticals into navigable waters of the United States and into waste water treatment plants (WWTP) by pharmaceutical manufacturing facilities.

In the future, EPA will continue to collaborate with agencies such as the FDA, USGS, CDC, and USDA to share information that may help in: (1) developing ambient water quality standards and criteria; (2) developing drinking water regulations; (3) assessing increasing antibiotic resistance; (4) developing effluent guidelines; and to share technology related to the development of analytical methods and treatment technologies. Additionally, internal collaboration of EPA's Program Offices and Regions in the future is important to: (1) develop and validate analytical methods for detection and quantification of PPCPs; (2) determine additional research needs; and (3) develop guidance on how to move forward until risk assessments for these types of contaminants are available.

***The EPA Regional Perspective—Why Pharmaceuticals in the Environment  
Are an Emerging Science Issue to EPA's Regions***  
**Bobbye (Barbara M.) Smith, U.S. EPA**

Following the EPA National Regional Science Council identification of PPCPs as a science need on which EPA should focus, a cross-Regional team on PPCPs was formed. The Regions identified examples where research was currently underway to investigate PPCPs.

Region 1 (New England) has developed a high performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) method for steroid hormones and other endocrine disrupting chemicals (EDCs) in water within the context of a study of 40 WWTPs in Connecticut, Maine, and Vermont. The Region also has awarded a grant to the Northeast Recycling Center to evaluate approaches to dispose of used consumer drugs and a grant to Hospitals for a Healthy Environment to address hospital pharmaceutical waste.

Region 3 (Mid-Atlantic) is working with the State of Virginia to identify the potential causes of intersex fish found in the south branch of the Potomac River. Scientists are using vitellogenin (VTG), a protein normally only expressed in egg-laying females, gene expression assays to assess the presence of estrogenic EDCs. The presence of VTG gene expression in the livers of males and juvenile fish indicates that the organism has been exposed to estrogenic EDCs. Region 3, concerned about antimicrobial veterinary pharmaceuticals and their effects on antibiotic resistance in environmental bacteria, is supporting an ORD project to investigate the environmental consequences of the use of veterinary antimicrobials.

Region 5 (Great Lakes) is developing analytical methods for surfactants, specifically alkyl and nonyl phenols and their ethoxylates, in collaboration with ORD. The Region is developing data that will support

the water quality criteria for some Great Lakes states. Additionally, the Region is working with ORD to correlate chronic toxicity values using classic toxicity bioassays, to the new generation of gene expression assays, so that gene expression can be linked to whole organism toxicity. EPA, USDA, USGS, and the Metropolitan Water Reclamation District of Greater Chicago (MWRDGC) are collaborating on a project to characterize the levels of a number of persistent, bioaccumulative, or toxic substances in aqueous and sludge samples throughout the Calumet Water Reclamation Plant. This study is funded through ORD's Regionally Applied Research Effort program. The study's objectives also include establishing a collaborative partnership among EPA, USDA, USGS, and MWRDGC and enhancing the analytical capabilities of participating laboratories. The study will initially focus on mercury, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers, alkylphenol ethoxylates (APEOs), PPCPs, and hormones. To date, two intensive sampling events have taken place at the Calumet plant in March and August 2005. Sampling at the Calumet plant will continue in late 2005 or early 2006.

Region 8 (Mountains and Plains) is funding a study of the relationship between WWTP effluent and the effects of EDCs on the native fish population. In addition to histology studies that have shown visual evidence of reproductive disruption in native white suckers, sites downstream of certain WWTPs displayed a sex ratio skewed toward females that would not be expected in a natural population. Additionally, intersex fish were found only downstream from the sampled WWTPs. As a result of this research, a multi-agency, multi-state, multi-stakeholder program entitled the Consortium for Research and Education on Emerging Contaminants has been formed and will hold a workshop in the near future. Anyone interested in participating should contact Patti Tyler, the Region 8 Regional Science Liaison.

Region 9 (Pacific Southwest) has been active in describing EPA's EDC and PPCP research agendas to multiple stakeholder groups for several years. In addition to training Region, state, and tribal personnel on gene expression EDC exposure assays, the Region is currently participating in a technology transfer of gene expression exposure tools to the State of California. Further, dischargers in Region 9 took part in an ORD-sponsored VTG gene expression study of 50 WWTP effluents across the United States to explore the efficacy of the new generation of gene expression exposure assays.

Region 10 (Pacific Northwest) is increasingly involved in assessing and dealing with impacts of rapidly expanding large-scale agricultural CAFO facilities, especially in southern Idaho and rural areas of Washington and Oregon. Detectable ground water contaminants traceable to such CAFOs include estradiol and sulfa drugs administered as veterinary pharmaceuticals. Aquaculture and mariculture also are very important to Region 10. Medications and other chemicals used in such finfish and shellfish culturing facilities are becoming a public perception issue regarding pollution of water, as well as the food products. The large cruise ship industry has enjoyed extremely rapid growth in Region 10. At the request of the State of Alaska, Region 10 took part in a recent scientific assessment of cruise ship wastes in Alaska waters, which ultimately recommended that PPCPs be considered as potentially significant emerging contaminants of concern to marine receiving waters. The Regional Laboratory also is developing the capacity to perform gene expression assays (e.g., for VTG).

The Regions need the science to answer the following questions: (1) Is there evidence of harm to human health or the environment at PPCPs levels that are detectable? (2) What are the sources of PPCPs in the environment? (3) Can PPCP sources be controlled or reduced? (4) What are the most important PPCPs to monitor? (5) What existing analytical methods should be used? (6) What is known about PPCP fate and transport? (7) Are there valid exposure and/or effects tests? To answer these questions, Regions need methods to measure biological exposures and effects as well as analyze chemicals. Additionally, the science of PPCP modes of action, pathways, and fate and transport needs to be explored. The links between new tools and human health and environmental outcomes need to be developed.

***Overview of Science Involved With Pharmaceuticals: A Perspective From the U.S. EPA***

**Christian Daughton, U.S. EPA**

PPCPs were first investigated as environmental pollutants in a concerted effort in Europe in the 1980s. It is important to note that PPCPs are not truly “emerging” pollutants; it is the understanding of the significance of their occurrence in the environment that is beginning to develop. The overall issue comprises numerous facets that involve the expertise of a broad spectrum of disciplines ranging from human health to ecology. There are thousands of distinct chemical entities with numerous (and increasing) therapeutic classes and end uses, a large number of which possess very high biological activity. Two classes of therapeutics that have received the most attention are the antibiotics, with the potential for resistance selection among pathogens, and steroidal hormones, which overlap with EDCs. For the plethora of other classes, however, little is known regarding the potential for effects. In general, PPCPs are not regulated water pollutants, and the few pollutants that are regulated are just a fraction of the chemical stressors to which organisms can be exposed on a continual basis.

Although most pollutants are not new to the environment, two major sources for pollutants are new: (1) chemicals newly introduced to commerce (e.g., new medications or pesticides); and (2) new anthropogenic processes (e.g., gallium arsenide quantum dots). Previously unrecognized pollutants can be brought to the attention of researchers as a result of new advances in chemical analysis (e.g., “nontarget” identification), the increased ability to detect existing pollutants at ever-lower concentrations, and the exploration of environmental areas not previously considered (e.g., foods as a significant source of acrylamide). There is no reason to believe that PPCPs have not existed in the environment for as long as they have been used commercially. Additionally, conventional priority pollutants (e.g., highly halogenated organics such as DDT and PCBs) are only a small part of the potential risk to the environment and living organisms. Less than 3 percent of commercially available substances and less than 1 percent of the known universe of 26 million chemicals currently are regulated or inventoried worldwide. Additionally, the number of chemicals that potentially can be synthesized from known chemicals is virtually limitless. Only compounds targeted for monitoring have the potential for being identified and quantified, and those compounds not targeted will elude detection. The spectrum of pollutants identified in a sample represent only a portion of those present, and they are of unknown overall risk significance.

Environmental exposure to PPCPs occurs as a result of excretion of the parent chemicals, their metabolites, or transformation products; disposal of expired or unwanted PPCPs into toilets, drains, and trash; leaching from municipal landfills; CAFO runoff; agriculture spraydrift; direct discharge of raw sewage; and transgenic production of proteinaceous therapeutics by genetically altered plants. The portion of PPCPs in the environment originating from disposal versus excretion, however, is not known. There are many ramifications to the presence of PPCPs in the environment: (1) Exposure to nontarget organisms could be significant. (2) Continual input via treated sewage allows PPCPs to be persistent despite short half-lives. (3) Aquatic organisms can suffer continual exposure. (4) The potential exists for subtle effects (e.g., neurobehavioral change) at even ppb levels ( $\mu\text{g/L}$ ). (5) The potential exists for inhibition of aquatic defensive mechanisms (e.g., efflux pumps). (6) There is a great challenge in identifying the many unknowns associated with effects from simultaneous exposure to low-levels of multiple chemical stressors over long periods of time. (7) The potential for additive (i.e., cumulative) and interactive (i.e., synergistic) effects from multiple exposure exists. Additionally, the toxicity of complex environmental mixtures poses major unanswered questions.

Bioconcentration of PPCPs is a possible new paradigm. Although their higher polarity would seem to preclude bioconcentration for most PPCPs, certain medications, despite their low lipid solubilities, are being detected in aquatic tissues in concentrations enriched from those in the ambient water. This is perhaps partly a result of drugs being designed to take advantage of gaining intracellular access via active transport. Understanding the subtle effects of PPCPs on organisms is an important aspect of investigation.

Two important questions to consider are: (1) Could immediate biological actions on nontarget species be imperceptible but nonetheless lead to adverse impacts as a result of continual accretion over long periods of time? (2) Could subtle effects accumulate so slowly (perhaps seeming to be part of natural variation) that major outward change cannot be ascribed to the original cause? Effects that are sufficiently subtle that they are undetectable or unnoticed present a challenge to risk assessment; therefore, advances in developing and implementing new aquatic toxicity tests that can detect such changes are required.

Although there are growing pressures to reuse wastewaters for drinking, there are increasingly smaller recycle loops, and the ever-shortening spatial and temporal hydraulic connectivity between point of wastewater discharge and point of use for drinking will pose serious challenges for ensuring human safety and for framing how risk is perceived by the consumer. Negative images in the consumer's mind cannot necessarily be erased or corrected by more or even better science; studies show that additional supportive data often serve to exacerbate preconceived negative images. Effective communication between scientists and the public is another important factor in managing the challenge of pharmaceuticals in the environment.

## **FATE, EFFECTS, AND OCCURRENCE OF PHARMACEUTICALS IN THE ENVIRONMENT**

### **Session A**

**Moderator: Angela Page, U.S. EPA**

#### ***Occurrence, Environmental Fate, and Exposure Assessment of Selective Serotonin Reuptake Inhibitors (SSRIs) in Aquatic Environments***

**Kevin Armbrust, Office of the State Chemist, Mississippi State Chemical Laboratory**

The Mississippi State Chemical Laboratory's research plan is to determine the environmental fate of pharmaceuticals via experiments similar to those required for pesticide registration (e.g., hydrolysis, photolysis, aquatic metabolism, etc.), measure parent and major degradation product occurrence in wastewater effluent and downstream receiving water, and determine acute and chronic impacts to *Ceriodaphnia* and reproductive impacts to *Gambusia* in cooperation with scientists at the University of Georgia. The laboratory chose to focus on the five most commonly prescribed SSRIs: fluoxetine, sertraline, fluvoxamine, paroxetine, and citalopram. Sertraline is the most heavily prescribed and at the highest dose. The factors the laboratory investigated were solubility in water, the octanol-water partition coefficient, negative logarithm of the acid dissociation constant ( $pK_a$ ), and hydroxyl radical rate constant; data support the assumption that volatility is negligible. The degradation experiments included hydrolysis (rate and products measured), aqueous photolysis (rate, quantum yield, and products measured), and ready biodegradability (rate and products measured). Additionally, simulated sunlight was added to the experiments because sunlight is important to degradation, especially in shallow water environments.

The results of the experiments indicated that all compounds, with the exception of paroxetine, were stable under all conditions. The common trend for all medications was to rapidly partition into sediment and stay persistent in the sediment for 30 days. Sertraline binds more strongly to soil than the other SSRIs tested, paroxetine was most reactive to the hydroxyl radical, and citalopram was the most interesting from a degradation standpoint. The general trend of the environmental fate of all SSRIs tested indicated that they strongly adsorb to soil and sediment, are hydrolytically stable, and are relatively persistent; the exception is paroxetine. Exposure assessment models, therefore, would be driven by sorption and stability for persistent SSRIs. Additionally, the laboratory monitored influent, effluent, and upstream and downstream water and sediment of the Columbus Wastewater Treatment Plant in Columbus, Mississippi, using LC/MS/MS analysis. Citalopram, fluoxetine, and sertraline were detected in all samples in various concentrations at various time points over the course of several months. Norfluoxetine was detected in one influent sample. The next steps for the laboratory are to complete  $pK_a$  measurements, assess exposure

based on physical and chemical properties and degradability, analyze sediments, and validate methods for fish and mussel tissue.

***Occurrence and Fate of Antibiotics and Other Pharmaceutically Active Compounds  
During Transport to and During Drinking Water Treatment***  
**Howard Weinberg, University of North Carolina**

Chlorination is a common treatment process for drinking water disinfection in the United States. The chlorine residual that is maintained throughout the distribution system, however, can react with organic contaminants in the water. Hence, if the concentrations of the contaminants in drinking water are required, the residual must be quenched at the time of sample collection. This laboratory has developed quality-controlled analytical methods for antibiotics in source and finished drinking waters that enable the detection of concentrations as low as 20 ng/L. The laboratory is monitoring three drinking water treatment plants downstream of CAFO and municipal WWTP discharges. There are low levels of antibiotics found in the source water for all sites, and some antibiotics are persistent throughout the drinking water process. At a fourth drinking water plant, different types of filtration were analyzed and compared. Sand filtration has almost no effect in reducing the concentration of antibiotics, whereas granular activated carbon (GAC) filtration showed a significant reduction for some antibiotics but not all of them. Antibiotics were present in the finished water even after chlorination. A fifth treatment plant included two chlorination steps in its process. After the first chlorination, there was no change in the trimethoprim concentration. Erythromycin disappears completely before the second chlorination step. In addition, the fate of antibiotics as they move from WWTP discharges downstream is being evaluated through a simulated transport and photolysis reactor. The laboratory's reactor design includes a photolytic cell that converts some of the molecules into photodegradative products, some proportion of which is found in the sediment. By analyzing both the aqueous phase and sediments, the laboratory is able to perform a complete mass balance on the fate of the original antibiotics in this simulated environment.

Given that antibiotics appear to persist into some drinking waters, the use of more advanced treatment to effect their remediation is being explored. This includes the use of ultraviolet (UV) photolysis at different intensities and also the additive use of hydrogen peroxide to achieve a hydroxyl radical-initiated oxidation process. The rates of reaction determined under controlled conditions are pH dependent, as might be expected from the multiple  $pK_a$  values of some of the pharmaceutically active compounds. The establishment of rate constant curves for different pharmaceutical products may make it possible to adjust the treatment process to control, manage, and/or degrade these compounds.

In summary, in spite of photodegradation and sediment transfer, antibiotics are reaching drinking water plants. Whereas GAC filtration is quite an effective measure for reducing the levels of these and other active constituents during the treatment process, medium pressure UV, the most commonly employed mode of photolysis used for some remediative processes, is only partially effective in reducing the levels of the source compounds. Subsequent chlorination in the treatment process produces some chlorination byproducts that persist at low concentrations in tap water. Because of the presence of antibiotics in the receiving streams from WWTPs, the laboratory also is investigating if, in addition to their persistence in downstream surface waters, the antibiotics may be contributing to antibiotic resistance in microbial organisms, particularly if they are found to concentrate in the sediment phase.

***Occurrence and Fate of High Volume Pharmaceuticals in Wastewater Impacted Environments***  
**Mark Benotti, State University of New York at Stony Brook**

The objectives of this research project are to: (1) develop LC coupled with time-of-flight (ToF) MS methodology for the analysis of pharmaceuticals in wastewater-impacted environments; (2) determine occurrence of selected pharmaceutically active compounds (PhACs) in Long Island groundwater; (3)



elucidate processes governing compound mobility (e.g., sorption or degradation); (4) compare PhAC occurrence and fate between estuarine surface water and groundwater; and (5) determine which compounds make the best wastewater tracers in either environment. LC-ToF-MS technology has been applied to investigate: PhACs in groundwater, estuarine surface water, and effluent; estrogens and APEOs in water and sediments; the removal of emerging contaminants during reverse osmosis wastewater treatment; and polyethoxylated homologous series of surfactants and surfactant metabolites.

In the groundwater component of this project, two sets of Long Island groundwater wells were sampled and analyzed for PhACs. The first set was comprised of 52 wells with an average depth of 250 feet. Single samples analyzed from these wells and concentrations were generally lower than median concentrations of similar compounds reported in the USGS National Reconnaissance Survey of U.S. streams and rivers. The notable exception to this was fluoxetine, which is found in a higher concentration in groundwater in Long Island as compared to the national median. The second set was comprised of 20 wells with an average depth of 66 feet and 5 wastewater effluents. These wells and effluents were sampled in triplicate and analyzed for the same PhACs. In this shallower group of wells, the mean concentrations of the battery of PhACs also were lower than the USGS National Reconnaissance results, whereas concentrations in STP effluent were higher. When comparing the first and second set of wells, the median concentration of each PhAC was slightly lower in the deep wells and roughly an order of magnitude lower than the USGS National Reconnaissance results.

Looking at the transport of PhACs through a well-defined well-field at a nursing home with an on-site wastewater treatment plant and comparing observed occurrences to laboratory sorption studies, it was found that: compounds that moved well with groundwater are not strongly adsorbed; compounds exhibiting the best mobility through the well-field have low adsorption coefficients ( $K_{DS}$ ); PhACs that do not move well with groundwater are either strongly adsorbed or degraded; and some negligibly transported compounds have high  $K_{DS}$  (suggesting adsorption) and some have low  $K_{DS}$  (suggesting microbial degradation). In Long Island groundwater, sulfamethoxazole and carbamazepine likely make the best molecular tracers of wastewater, as they are ubiquitous throughout the two sets of wells, migrate well through the nursing home well-field, and do not strongly adsorb to aquifer material.

A parallel project investigated several sampling sites in New York's Jamaica Bay, an estuary where wastewater is the primary source of freshwater during dry conditions. Simple mixing curves show that for compounds with little removal, PhAC concentrations throughout the bay can predict effluent concentrations (y intercept) and seawater endmember salinity (x intercept). For some compounds, mixing curves plot below the linear mixing line, suggesting removal. Laboratory microbial degradation experiments, however, showed that most compounds are resistant to microbial degradation on the time scale of water mixing within the bay. In Jamaica Bay, caffeine, cotinine, and paraxanthine make the best tracers as their concentration range was highest, they resisted microbial degradation on the times scales of mixing within the bay, and their dynamic range (i.e., ratio of concentration to detection limit) was highest.

The project conclusions are as follows: (1) LC-ToF-MS is a powerful tool for the analysis of PhACs in wastewater-impacted systems. (2) Pharmaceuticals are present in susceptible Long Island groundwaters at concentrations typically lower than those previously reported for impacted U.S. streams and rivers. (3) Groundwater concentrations are highest in shallow wells and/or adjacent to point source discharge. (4) Mobility in groundwater is limited by adsorption and degradation. (5) Compounds that migrate best through groundwater have low  $K_{DS}$  (measured) and biodegradation rates. (6) Carbamazepine and sulfamethoxazole appear to be the best tracers of wastewater in subsurface environments. (7) Caffeine and paraxanthine are less persistent, but at certain sites may serve as tracers because of their local high loading. (8) In Jamaica Bay, most PhACs are relatively persistent over the hydraulic residence time-scale of the bay. (9) Most compounds do not degrade extensively within 4 weeks. (10) Caffeine, paraxanthine, and cotinine are possible estuarine wastewater tracers measured in greatest abundance.

***Detection and Fate of Environmental Estrogens in Wastewater Impacted Surface and Groundwater***  
**Bruce Brownawell, State University of New York at Stony Brook**

Mammals excrete steroid estrogens primarily as water-soluble glucuronide. It is important to understand the distribution of free steroids and their conjugates in the aquatic environment, because glucuronide can release free estrogens via hydrolysis in effluent; therefore, soluble estrogen conjugates could act as a source of estrogens in aquifers or groundwater-fed streams. The objectives of this research project were to: (1) develop methods for determining intact conjugates of steroid estrogens in wastewaters and wastewater impacted groundwaters; (2) assess persistence and mobility of conjugates in sewage treatment systems and groundwater environments; (3) assess the mobility of APEO metabolites in groundwater; and (4) develop methods to determine steroid estrogens in sediments and soils to better understand fate and transport.

The laboratory developed a method for analysis that removes much of the background matrix at each step so that there is improvement in matrix suppression and isobaric interference. After loading the sample in an Oasis<sup>®</sup> Hydrophilic-Lipophilic Balance cartridge, the free estrogens are extracted with ethylacetate. Next, acidic and weakly basic interferences are removed and a selective extraction is performed. Another cleanup over an anion exchange column is completed, and the sample is analyzed via reversed-phase HPLC/MS/MS. The estrogens undergo further purification by an immunosorbent method previously developed in the laboratory. As a result of this method, detection limits are now useful. The findings using this method indicate that there are not many glucuronides found in sewage influent, signifying that they are hydrolyzed to form free estrogen before arriving at the plant.

Another project involved a Cape Cod multi-family septic tank and illustrated that effluent from the septic tank entered several well clusters within a couple of days to less than 1 week. This is short-term, short-range transport of a number of wastewater contaminants, including estrogens and APEOs. The plume extends along the groundwater table. Additionally, the laboratory developed a method for looking at estrogens in solid samples and has applied it to sediments that have a high organic matrix. The method applies cleanup over an HPLC diol column before running the sample over an immunoaffinity column. The laboratory analyzed sediments from a Jamaica Bay, New York, sewage estuary and found that there was a good correlation between estrogens and nonylphenol polyethoxylates (NPEO) and that the ratio is about the same ratio seen in surface water. Additionally, the levels of estradiol and estrone were as potent as NPEO.

In conclusion, steroid estrogen conjugates, especially the glucuronides, are rapidly transformed (in part to free estrogens) before reaching STPs, where they are further degraded; conjugates also are rapidly transformed in anaerobic septic tanks. It does not appear that conjugated estrogens represent a large source of steroid hormones to receiving waters; whether conjugates or other PhACs of interest are more persistent still needs to be determined. Measurements of glucuronide conjugates in wastewater require immediate acidification of samples; other poisons do not stop activity of extracellular hydrolases in wastewater. Although neither steroid hormones nor APEO metabolites are observed to be mobile over long distances in oxic groundwater, they do migrate, particularly the APEO metabolites, tens of feet in an anaerobic septic tank plume. The extent to which septic plumes act as a source of organic wastewater contaminants to nearby receptors (e.g., ponds and wells) merits further investigation. Understanding the mechanism of rapid degradation of organic wastewater contaminants along oxic flowlines close to septic tanks may help in better design of onsite sewage treatment systems.

## **FATE, EFFECTS, AND OCCURRENCE OF PHARMACEUTICALS IN THE ENVIRONMENT Session B**

**Moderator: Cynthia Nolt-Helms, U.S. EPA**

### ***Mechanisms of Tetracycline Resistance Development in the Environment as Detected by Real-Time PCR***

**David Graham, University of Kansas**

This laboratory combines molecular biology and multiple scale ecological biology to investigate: (1) resistance genes at cattle feedlots versus antibiotic use strategy; (2) *in situ* development of resistance versus antibiotic loading rate; and (3) resistance gene decay and organism die-off in surface waters. The laboratory's experimental program studies the fate and effects of tetracyclines and fluoroquinolones (FQs) in aquatic systems and investigates how to combine water chemistry and classical microbiology with various molecular techniques to assess relevant scenarios. Specific experiments with tetracycline have included: (1) fate and resistance versus antibiotic use strategies in cattle feedlots, which includes the observation of resistance in waters below feedlots; (2) resistance development in mixed-community, non-flowing impoundments, investigating potential impacts on microbial communities and plants in surface waters; and (3) resistance retention and decay in different receiving waters from watersheds with variable land uses. The third experiment includes exploration of gene decay rates in aquatic systems and factors that affect decay rate.

Results indicated that there were two to three orders of magnitude more genes associated with tetracycline resistance in high antibiotic-use feedlots. Statistical analysis was performed on more than 16 different parameters that could possibly affect the retention of resistance genes in a particular lagoon. There was a positive correlation with increased resistance genes and the following parameters: use rate and pattern; lot size; head count; and volatile suspended sediments. Additionally, there was a negative correlation between length of day and sun hours. The laboratory concluded that feedlot operations strongly correlate with resistance gene copy numbers in lagoons, although they also found that measured ambient lagoon tetracycline levels only weakly correlate with detected resistance gene numbers. These results led the investigators to further explore where resistance is actually developed in animal-to-water systems; how long resistance persists once in the environment; and if antibiotic use has ancillary effects on other elements of aquatic ecosystems.

The major conclusions of the project, based on the tetracycline data, are as follows: (1) Feedlot antibiotic use practices significantly impact the resistance genes in downstream waters, but resistance is gained primarily in the animal, not in water. (2) Measured tetracycline levels tend not to correlate or only weakly correlate with resistant gene or organism numbers. (3) Resistance genes and organisms decay rapidly in natural waters, but resistance can transiently increase as a result of local ecological effects. (4) Light increases the rate of decay of resistant organisms and genes. The management implications of this research are as follows: (1) Antibiotic use should be tightly controlled in agricultural operations because use pattern affects resistance gene and organism numbers downstream. (2) Water and wastewaters should be contained onsite in treatment units that maximize mixing and light penetration (e.g., mixed lagoons). (3) It is beneficial to monitor genes (or organisms) instead of the antibiotics themselves to assess exposure and impacts.

### ***Fate, Attenuation, and Effects of Fluoroquinolone Antibacterials in Aquatic Systems***

**Charles Knapp, University of Kansas**

FQs are a class of broad-spectrum antibacterial agents that act through the direct inhibition of DNA-gyrase in host organisms and primarily target Gram-negative bacteria, but also affect Gram-positive

organisms to some extent. There are greater than 10 commercially available FQs that are generally very effective and include ciprofloxacin, used for human clinical purposes, and enrofloxacin, found in agricultural use. The objectives of the research project are to: (1) develop new methods for detection of FQs and effects of FQ exposure on resistance in the environment; (2) assess FQ fate under different aquatic conditions in laboratory-scale systems; (3) determine FQ fate and effects in mesocosm-scale systems; and (4) perform toxicity tests on aquatic organisms. Toward these objectives, the laboratory developed new methods using LC/UV-MS techniques for enrofloxacin and ciprofloxacin that have high sensitivity and detection limits ( $< 1 \mu\text{g/L}$ ), which led to the discovery of new breakdown products. One key observation is that a primary breakdown product of enrofloxacin degradation is ciprofloxacin; therefore, it is necessary to monitor both to assess net FQ exposure in effects studies.

Four laboratory-scale studies on enrofloxacin and ciprofloxacin fate were performed to assess the effects of dissolved organic carbon (DOC), particulate organic carbon (POC), pH, light intensity, and biotic activity. Results revealed that enrofloxacin and ciprofloxacin are highly sensitive to light but are not impacted by DOC, indicating that it is necessary to regulate light supply in field-scale studies to control exposure time. Additionally, enrofloxacin and ciprofloxacin are affected by POC. Because ciprofloxacin readily binds to particles, it is possible to filter it out. The researchers extrapolated the laboratory-scale results and applied their finding to design field-scale experiments. In these experiments, although enrofloxacin degraded as a function of light supply, some ciprofloxacin formed as a result of this degradation but only significantly in the tanks simulating a partially shaded light source. A surprising result was that there was no major change in aquatic community diversity following addition of enrofloxacin. The major findings of the project include: (1) Enrofloxacin and ciprofloxacin are photo-sensitive and have low residence times in light-exposed aquatic systems. (2) Point enrofloxacin addition appears to have minimal impact on water chemistry and whole community conditions. (3) No increased FQ resistance was noted using molecular techniques under the conditions assessed. (4) It is possible that effects may differ in less light-exposed (i.e., deeper) aquatic systems or scenarios with continuous release and/or exposure. (5) Effects can be seen at higher concentrations in some aquatic organisms.

***Adsorption of Beta-Blocker Anti-Hypertensive Pharmaceuticals to a Range of Mineral Surfaces***  
**Tohren Kibbey, University of Oklahoma**

The objectives of this research project were to: (1) study the adsorption to individual mineral components of a complex natural material to better understand adsorption to the material as a whole; and (2) study the adsorption of beta blockers. Beta blockers have been detected at  $\mu\text{g/L}$  concentrations in the environment, but there has been little reported adsorption data for environmental sorbents. The three beta blockers studied in the project—propranolol, metoprolol, and nadolol—all have very high aqueous solubilities, but vary in their hydrophobicity, with propranolol being moderately hydrophobic (as indicated by  $\log K_{ow}$ ) and the other two being moderately hydrophilic. All three compounds are positively charged at neutral pH. Seven minerals were selected for study based on the content of Canadian River Alluvium (CRA), a natural material collected from the alluvial channel of the Canadian River in Norman, Oklahoma. The minerals selected included a quartz sand, two feldspars, ilmenite, magnetite, hematite, and tourmaline, all components identified in the CRA.

Experimental results indicate that adsorption isotherms in the presence of the CRA and each of the minerals studied were near-linear for all three compounds. Adsorption affinity of propranolol was greatest for all but two of the sorbents, a result that is consistent with the difference in hydrophobicity of the compounds. Comparison between the solution pH of each experiment and the point of zero charge (PZC) for each mineral indicated that electrostatic effects do not completely predict differences between adsorption on the sorbents examined: adsorption occurred to magnetite and hematite below their PZCs (i.e., both mineral and beta blocker were positively charged), and adsorption to the quartz and feldspars was generally lower than adsorption to tourmaline and ilmenite, despite the lower PZCs of quartz and

feldspar relative to the experimental conditions for those minerals. Overall, results reveal that adsorption of beta blockers to many of the surfaces studied is high enough to influence transport, and the adsorption extent is comparable to quinolone antibiotics at neutral pH.

***Pharmaceuticals and Personal Care Products as Environmental Contaminants (1):  
Preliminary Environmental Risk Calculations and Method Development for Analysis  
in Environmental Media via GC/MS***

**Lynn Roberts (presented by Kevin Bisceglia), The Johns Hopkins University**

The objectives of this research are to: (1) conduct a preliminary environmental risk assessment (ERA) by compiling data on pharmaceutical usage, occurrence and potential ecotoxic risk; and (2) develop GC/MS methods for selected PPCPs that are easy to perform, highly reproducible, robust, and amenable to the analysis of different matrices (e.g., surface water, drinking water, and wastewater).

To achieve the first objective, a detailed usage, occurrence, and ecotoxicity database was developed for the highest volume (i.e., top 200) pharmaceuticals in the brand name, generic, over-the-counter, and hospital categories for the years 1999-2002. Usage data were used to compute expected introductory concentrations (EICs) according to FDA guidelines, and toxicity data, obtained from EPA's ECOTOX database or estimated using EPA's Ecological Structure Activity Relationships (ECOSAR) program, were used to compute probable no-effect concentrations (PNECs). The preliminary ERA indicated that pharmaceuticals are extremely diverse; more than 50 therapeutic classes are represented in the 800 drugs considered. No correlation existed between EIC and pharmaceutical sales ranking, suggesting that many more pharmaceuticals could be of potential concern than were identified in this study. The majority (i.e., greater than 80%) of pharmaceuticals that potentially are present at measurable concentrations (i.e., > 10 ng/L) have not yet been sought by environmental researchers. EICs appear useful in providing order-of-magnitude estimates of concentrations encountered in sewage treatment plant influents. Preliminary calculations (using experimental and ECOSAR-derived toxicity data) indicate that as many as 10 percent of the pharmaceuticals considered in this study likely are to be of environmental concern. Our results suggest that the current FDA "trigger" of 1 µg/L for performing risk assessments on new pharmaceuticals may be insufficiently conservative, as some compounds exert chronic toxicity below that threshold.

In achieving the second objective, choice of derivatization agent, solvent, and reaction conditions were systematically tested, as were necessary sample clean-up procedures. SPE was explored as a pre-concentration step, and the selection of sorbent media, sample pH, and elution solvent identity was systematically investigated, as well. Highlights are as follows: (1) Two new multi-compound GC/MS methods were developed for a total of 52 acidic, basic, and neutral analytes. (2) The methods encompass a wide range of analytes from several different therapeutic classes and provide high sensitivity and good reproducibility. (3) The new method for derivatization of acidic compounds is particularly robust and performs best in acetonitrile:water mixtures, thus eliminating the need for solvent blowdown and associated losses. (4) Good recoveries were found using newer, polymeric SPE cartridges. (5) The SPE method has proven to be reproducible and exhibits minimal interference when extracting target compounds from waters high in natural organic matter. These methods have been demonstrated to perform well in highly complex matrices, such as raw and finished wastewater, as indicated by recoveries of isotopically labeled surrogates or laboratory-fortified field samples.

***Pharmaceuticals and Personal Care Products as Environmental Contaminants (2):  
Biodegradability Studies and Occurrence in Sewage Treatment Plant Influent and Effluent***  
**Lynn Roberts (presented by Jim Yu), The Johns Hopkins University**

Two objectives of the research project are to: (1) determine the occurrence and loading of pharmaceuticals and antiseptics into municipal WWTPs; and (2) evaluate the adequacy of current wastewater

treatment practices in removing pharmaceuticals and antiseptics. Using the method described in the previous presentation, the laboratory sampled four STPs with different treatment technologies on the Northeastern U.S. seaboard (Yonkers, NY; Philadelphia, PA; Baltimore, MD; and Washington, DC) with collective influent flow greater than 1.5 billion gallons per day. Results of these experiments indicated that 38 of the 52 compounds in the analyte suite were detected in one or more of the WWTPs, at concentrations as high as 3,000 ng/L. Although most compounds found in STP influents were detected at all sites examined, concentrations differed from site to site. Certain PPCPs (diclofenac, amitriptyline, trimethoprim, labetalol, carbamazepine, metoprolol, primidone, propranolol, diltiazem, and acyclovir) were relatively persistent, with little removal (< 50%) at the STPs sampled, and PPCP removal efficiencies varied at different STPs. Preliminary results indicate that removal efficiency correlates with STP solids retention time.

The objectives of the biodegradation portion of the research project are to: (1) examine the biodegradability of selected PPCPs; and (2) examine biodegradation behavior under different environmental conditions (e.g., varied electron acceptors and microbial communities). The experiments were conducted under aerobic and anaerobic conditions and investigated a suite of prescription and over-the-counter (OTC) medications as well as antiseptics. It was found that valproic acid, ibuprofen, phenobarbital, and acetaminophen exhibited biotransformation only under aerobic conditions; ketoprofen, naproxen, and secobarbital were substantially (> 60%) biotransformed under all conditions; and phenytoin, diclofenac, and 5-fluorouracil do not readily biotransform (< 60%) under any condition. All antiseptics readily biotransformed (> 60%) under all conditions tested. From the laboratory studies, it was concluded that: aerobic conditions are more favorable for biotransformation than anaerobic conditions; iron-reducing conditions were the least favorable; biosorption did not play an important role for the compounds tested; the different aerobic microbial communities (activated versus primary) exhibited similar biotransformation behaviors, whereas the different anaerobic microbial communities (nitrate versus iron) had dissimilar behaviors for some compounds; and biotransformation efficiency was not sensitive to initial concentrations.

***Endocrine Effects of Selective Serotonin Reuptake Inhibitors (SSRIs) on Aquatic Organisms***  
**Marsha Black, University of Georgia**

SSRIs, such as fluoxetine, have been detected in surface waters, and fluoxetine, sertraline, and their metabolites have been detected in fish tissues. This is problematic because pharmaceuticals are designed to have a biological effect and these effects on nontarget organisms are mostly unknown. Not only are aquatic organisms exposed throughout their lifetime, there is also the potential for multigenerational exposure. Although little is known about the persistence and fate of pharmaceuticals in the environment, SSRIs are known to promote spawning in mollusks. Given these facts, the overall research plan was to determine the environmental fate of SSRIs, measure parent and major degradation products in wastewater effluent and downstream receiving water, and determine acute and chronic impacts to aquatic organisms. All toxicity tests followed EPA protocols.

The results of the experiments showed that SSRIs are acutely toxic to *Ceriodaphnia dubia* (a macroinvertebrate) and Western mosquito fish. Additionally, fluoxetine affects fish behavior, including: uncoordinated swimming; lethargy and lack of response to stimuli; and decreased aggression and interaction between individuals. Fluoxetine delays sexual development in fish and also delays development, including forelimb formation and tail resorption, and metamorphosis in frogs. Reduced mass and limb malformations in frogs were observed with chronic exposure to fluoxetine, and both effects occurred at environmentally relevant concentrations. Implications of these observations include the possibility of increased predation, desiccation in frogs, decreased reproductive success, and eventual population decline.

## **HAZARDS FROM WASTE PHARMACEUTICALS: DETERMINING TOXICITY AND CHEMICAL ANALYTICAL METHODS FOR DETECTION**

**Moderator: Tammy Jones-Lepp, U.S. EPA**

### ***Overview of a Framework for Assessing the Hazards of Human Pharmaceuticals in the Environment From a SETAC Pellston Workshop***

**Marsha Black, University of Georgia**

The members of a workgroup from a Society of Environmental Toxicology and Chemistry (SETAC) Pellston Workshop were tasked with placing biological effects into an overall framework for assessing pharmaceuticals and their impact on the environment. Historically, ecological risk assessments for human pharmaceuticals were generally a prediction of potential environmental concentrations or short-term lethality assays with little or no consideration of potential long-term toxicity, secondary impacts (e.g., via bioaccumulation), or the effects of metabolites. The challenge is managing thousands of chemicals, some of which could have significant chronic toxicity, while trying to protect all microbial, plant, and animal species, with uncertainty about the most sensitive phyla. The workgroup proposed a solution that includes: testing a set of reference active pharmaceutical ingredients (API) with defined mechanisms of action on microbes, plants, and animals representative of phyla of concern; defining logical suites of tests for untested APIs to estimate risk; and conducting *post hoc* environmental monitoring to assess the robustness of risk prediction. The overall approach comprises a research phase, a hazard identification phase, and a monitoring phase. A focused, technically rigorous approach emphasizes testing based on mechanism of action, including identification of a test “tool box” (e.g., species, endpoints) using model APIs and diverse phyla; selection of chemical-specific test suites based on physico-chemical properties and assessment scenario; and application of routine followup monitoring.

### ***Overview of ORD’s Aquatic Toxicology Research on Endocrine-Active Pharmaceuticals***

**Joseph Tietge, U.S. EPA**

ORD laboratories are engaged in variety of research projects with aquatic organisms that are relevant to the assessment of pharmaceuticals in the environment, specifically as they pertain to endocrine pathways. The broad objectives of these projects are to assess effects of chemicals on endocrine pathways in fish and amphibian species in laboratory studies and to evaluate exposure to endocrine active chemicals in the environment using field studies. The effects of chemical exposure on molecular, cellular, organ, organismal, and population endpoints are assessed and linkages are developed to predict effects at higher levels of organization and to diagnose the mode or mechanism of toxicity at lower levels of organization. When iterated, this information can be used to build libraries of toxicity pathways that cover various physiological systems of interest.

There are three major approaches being used by ORD. In the first approach, two short-term screening assays are being developed to identify chemicals that affect hormone (e.g., estrogen, androgen, and thyroid hormone) regulation and function using a variety of organismal, biochemical, and histological endpoints. One such assay utilizes the fathead minnow (*Pimephales promelas*) in a 21-day protocol to evaluate the effect of test chemicals on estrogen and androgen pathways, as determined by reproductive success, circulating sex steroid concentrations, gonadal histology, secondary sexual characteristics, and other biochemical endpoints. The basic protocol for this assay is complete and validation studies are currently underway. The other screening assay utilizes the metamorphic phase of the African clawed frog (*Xenopus laevis*) in a 14 to 21 day assay to evaluate the effects of test chemicals on thyroid function. Metamorphosis is a thyroid hormone-dependent event and perturbations of normal thyroid hormone homeostasis alter developmental rate and thyroid histology. This screening assay is also in the process of validation. In the second approach, partial and full life cycle tests are being developed to evaluate the effect

of chemicals on reproductive and developmental endpoints in a fish, the Japanese medaka (*Oryzias latipes*), and in an amphibian (*Xenopus tropicalis*). The intent of this research is to determine if EDCs result in transgenerational effects that are not detected in the preceding short-term screening assays. These tests, when fully developed and validated, may be used to better understand population-level effects. In the third approach, selected endpoints that were developed in both the screening and testing protocols are being used in field studies where naive fish are exposed to surface water discharges, such as effluents emanating from confined animal feeding operations and municipal wastewater treatment plants. These studies demonstrate that androgenic and estrogenic activities can be detected in surface water discharges using well-defined methods.

Taken together, these projects have advanced the basic understanding of endocrine disruption in aquatic organisms, help to meet Agency screening and testing requirements mandated through the FQPA and SDWA, and provide the Agency with tools to assess potential endocrine disruption in aquatic species in the environment. Additionally, the approach used by ORD for evaluating EDCs is amenable to assessing the impacts of pharmaceuticals to aquatic organisms, including identification of toxicity pathways, development of diagnostic endpoints relevant to a toxicity pathway, and constructing a rationale to understand source-to-outcome relationships.

***Analytical Methods for Measurement of Pharmaceuticals in Drinking Water and in the Environment***  
**Mike Meyer, U.S. Geological Survey**

The USGS performed a series of national reconnaissance studies of streams, groundwater, drinking water, and streambed sediment to determine the prevalence of emerging contaminants in areas susceptible to contamination from sources of human and agricultural waste (e.g., WWTPs, livestock operations, etc.). The USGS methods to determine occurrence of PPCPs in the environment are very similar to methods used by EPA, FDA, USDA, and NOAA, including liquid-liquid extraction and SPE. USGS uses its own standard sample collection procedures, however, for collecting a uniform representative environmental sample and has a meticulous QA/QC process in place. The research team is currently conducting an in-stream process study in two effluent-dominated streams (Boulder Creek, CO, and Four-Mile Creek, CO) to examine the transport and fate of pharmaceuticals and other emerging contaminants and determine differences in fish community structure and fish-health upstream and downstream of the primary contaminant source (i.e., WWTP). The national reconnaissance studies have shown that emerging contaminants are both a surface water and groundwater issue. In general, however, most classes of compounds are found more frequently and in higher concentrations in streams than in groundwater. In addition, streambed sediment also is a reservoir for emerging contaminants. Select compounds that were rarely present in stream water (e.g., fluoxetine, miconazole) were prevalent in streambed sediment. All WWTP effluents were found to contain a complex mixture of emerging contaminants, including antibiotics and other prescription pharmaceuticals, nonprescription drugs, fragrances, and other personal care products.

A study was conducted to determine the distribution of pharmaceuticals in soils where reclaimed water was used as a source of irrigation. The objectives of this study were to: (1) determine if the emerging contaminants present in the reclaimed water used for irrigation are also present in the receiving soil; (2) evaluate the behavior of pharmaceuticals in these irrigated soil; and (3) evaluate the potential of this practice for the dissemination of emerging contaminants to groundwater. Results document that irrigation with reclaimed water does lead to the presence of emerging contaminants in receiving soils. Concentrations can persist from one season to the next.

The methods the USGS are using to analyze pharmaceuticals and other emerging contaminants in the environment are generally evolving to MS/MS technology. The SPE-LC/MS method for human pharmaceuticals that previously only was available on a limited basis within the USGS is being transi-



tioned to become an agency-wide analytical method. In addition, the USGS method to analyze biogenic and synthetic hormones has evolved from gas chromatography (GC)/MS to GC/MS/MS, and the USGS antibiotic method has evolved from tandem SPE-LC/MS to online SPE. The USGS has also developed analytical methods for analyzing emerging contaminants in solids (e.g., soil, bed sediment, biosolids, etc.).

The USGS reconnaissance studies documented a wide distribution of emerging contaminants in the environment. Fate studies identified both conservative and nonconservative transport of emerging contaminants in streams. Irrigation with reclaimed water translated to concentrations of emerging contaminants in bulk soil. Further research is needed to determine treatment technology that provides the greatest reductions of emerging contaminants from solid and liquid wastes. In addition, more research is needed to identify and analyze environmental degradates of emerging contaminants. Information of such degradates will provide important information on the transport and fate of emerging contaminants and a better understanding of the ultimate environmental effects from the use of these compounds.

### ***Environmental Risk Assessment of Pharmaceuticals in the Environment***

**Chuck Eirkson, U.S. Food and Drug Administration**

The FDA is the primary federal agency for regulating foods and food additives, human and animal medications, cosmetics, and medical devices; therefore, it is the primary regulatory agency for PPCPs. The FDA's statutory authorities include the Food, Drug, and Cosmetic Act of 1938; the Public Health Service Act of 1944; and the National Environmental Policy Act of 1969. For major actions taken by the FDA, a categorical exclusion, environmental assessment, or environmental impact statement may be needed. The Agency's roles and priorities are to review all categorical exclusions and environmental assessments and determine appropriate follow-up. This could include the preparation of an environmental assessment, a finding of no significant impact, or an environmental impact statement.

Classes of actions that have been predetermined not to individually or cumulatively significantly affect the quality of the human environment are categorically excluded from preparing environmental assessments. Examples of categorical exclusions include action on original and abbreviated new human and animal drugs and biologics if there is no increase in use of the active moiety; approvals of original and abbreviated human drugs entry into aquatic environment of less than 1 ppb; action on medications and biologics for a naturally occurring substance if there is no significant change; and investigations on new human and animal medications. If, at the expected level of exposure, there is the potential for serious harm to the environment or if there is adverse effect on a species or the critical habitat of an endangered or threatened species, these are considered extraordinary circumstances, and categorical exclusions do not apply and an environmental assessment is necessary. Most FDA actions are categorically excluded. All analyses are made public.

The focus of an environmental assessment for the FDA includes: ecosystem protection; laboratory studies on invertebrates, fish, and plants at various trophic levels; measurement endpoints such as mortality, immobilization, reproduction, growth, and functional responses; and biogeochemical cycling (e.g., nitrogen, carbon transformation). There is a tiered approach to human fate and effects testing that incorporates several different types of studies. Physical-chemical studies include water solubility, dissociation constant, UV-visible absorption spectrum, melting temperature, vapor pressure, and octanol/water partition. Environmental fate studies include soil adsorption/desorption, degradation in soil, and degradation in aquatic systems. Acute or chronic effects studies may be conducted on a variety of organisms, depending on the level of concern determined by the comparative analysis of conservative estimates of exposure and effects. For veterinary products, aquatic effects studies are conducted with algae, *Daphnia*, and fish. Terrestrial effect studies are performed with microorganisms, terrestrial plants, and earthworms. Risk management may be used as needed.

The FDA has several ongoing collaborations with other agencies. The FDA is working with EPA's Office of Clean Water on the review and regulation of animal medications in effluents from aquaculture facilities. They are also collaborating with the USGS Toxic Program and EPA Field Offices on pharmaceuticals in the environment. Additionally, the FDA co-sponsored the Veterinary International Conference on Harmonization, confers with pharmaceutical manufacturers on improved methods to estimate environmental exposure levels, and monitors literature reports associated with PPCPs in the environment. The FDA completed a SETAC workshop on human pharmaceuticals and is working jointly with academia, other government agencies, and pharmaceuticals companies in planning another workshop with SETAC on veterinary medications in the environment. The FDA is also evaluating issues associated with the disposal of unused pharmaceuticals (i.e., pharmaceutical stewardship). For the more general issue of pharmaceuticals in the environment, it is necessary to acquire data on: background levels from natural sources (including humans); levels of mimics from industrial sources; and the minimum effect levels of pharmaceuticals. Additionally, a comparison of predicted and actual levels of pharmaceuticals is needed. Specific investigations also are needed on the effects of sunscreens and triclosan on the aquatic environment.

***An Informatic Approach To Estimating Ecological Risks Posed by Pharmaceutical Use***  
**Mitchell Kostich, U.S. EPA**

When prioritizing investigations of PPCPs in the environment, it is necessary to ask which pharmaceuticals are likely to have detrimental effects at environmental concentrations. Currently, there are more than 2,000 medications approved for use in the United States, the vast majority of which have little or no concentration or ecotoxicological data available. Chemical analysis is expensive, and acquiring chronic ecotoxicological data is even more rare and expensive; therefore, it is too costly to thoroughly study all pharmaceuticals in the near future. A rational way to "triage" pharmaceuticals for further analysis is needed. An informatics-guided approach breaks a problem down into components based on different data sets involved, different routes into the environment, and different likely modes of environmental impact (i.e., direct or indirect, including microbial resistance). EPA's Ecological Exposure Research Division is investigating the following areas in order of priority: human retail prescription medications; human OTC medications; human medications used predominantly in institutions; agricultural animals; aquaculture; and companion animals.

The approach being taken for prioritizing the first three categories (i.e., the human pharmaceuticals) is to calculate the likely worst-case scenario for each drug, assuming that the most likely toxicity is mechanism based. From this, the laboratory then predicts the highest likely environmental concentration using public usage data and physical properties to estimate excretion, dilution, and partition between matrices (assuming approximately 10 percent is flushed unchanged in every case). The data are normalized to express concentrations as human dose equivalents per volume. To investigate the effect on the environment, the laboratory calculates the PNEC for fish based on public data. The ratio of the highest likely environmental concentration to the PNEC is used to rank pharmaceuticals for the study. Although this method is semi-quantitative with subjective components, it focuses efforts on likely dangers and key uncertainties. The system is designed to be an updateable matrix database.

The pharmaceutical that displays the clearest scientific basis for concern appears to be ethynylestradiol (EE2). In many ways, it serves as a prominent example for pharmaceuticals that are likely to have ecological impact. For example, ecological concentrations are known to cause effects in the laboratory, and laboratory effects resemble morphological and reproductive changes occasionally seen in wild populations. EE2, widely prescribed with frequent and regular use, is unusually potent with a well-conserved method of action. Only part of total EDC activity, however, is a result of EE2; therefore, any remediation would likely need to be aimed more broadly. Furthermore, EE2 has several properties that set it apart from other pharmaceuticals and suggest that it might be a special case and not a good representative of

pharmaceuticals in general. EE2 is unusual in that it is designed to block a critical species function (i.e., reproduction). Indiscriminate administration of EE2 to the human population would eventually lead to extinction. It is not surprising, therefore, that indiscriminate administration to wild populations in the form of ecological contamination might cause similarly drastic population effects. Most other pharmaceuticals do not have this type of inherent toxicity (possibly antineoplastics and a few powerful teratogens but not beta blockers, SSRIs, or acetaminophen); the few that do are not nearly as widely nor regularly prescribed. Another pharmaceutical to consider is carbamazepine. Although the usage statistics are not particularly high and only a very small percentage is excreted unchanged, it is perhaps the most ubiquitous drug in the environment and survives drinking water treatment. Despite the fact that it is not one of the most prescribed medications, it is prescribed in chronic, high doses. Studies indicate, however, that the average consumption in drinking water over a lifetime is the equivalent of two regular doses; therefore, the likelihood of impact is very low.

### ***Identifying Chemical Compounds From Wastewater Discharges***

**Susan Glassmeyer, U.S. EPA**

It is advantageous to use chemical indicators to identify chemical compounds from wastewater discharges because of the rapid analysis times and the ability to discriminate human from animal fecal material. A suite of compounds with various physical and chemical properties may be more impervious to hydrological diversity; however, it is necessary to ensure that they are persistent enough to survive wastewater treatment, but not so recalcitrant that they become ubiquitous.

Surface water and sediment samples were collected at locations near several WWTPs: one upstream from each WWTP, one directly from the WWTP effluent, and two from downstream locations. Additionally, two control sites, in Michigan and Montana, were selected. The experimental approach included microbial and chemical analysis. Results indicated that bacteria concentrations tended to be lower in the WWTP effluent samples as compared to upstream and downstream samples, probably as a result of disinfection processes. Both of the bacterial strains tested for were detected at both of the reference locations; *Enterococci* at the Montana site exceeded recreational water guidelines. Of the 110 chemicals tested for, 78 were found in at least one sample, and 6 chemicals were found in at least 75 percent of the samples. The median number of chemicals detected in upstream samples was 10; in WWTP effluent, 35; in the first downstream location, 32; and 24 in the second downstream sample. At the reference locations, three chemicals with a very minute concentration were found in Michigan; none were detected in Montana.

Preliminary results demonstrate that pharmaceuticals and other chemicals survive wastewater treatment. Upstream background levels of many of the pharmaceuticals and wastewater compounds are low (especially when compared to the indicator bacteria) and indicate that they are not too ubiquitous. The downstream samples decrease at different rates for the various chemicals. Pharmaceuticals and other wastewater compounds may be able to be utilized as chemical indicators of human fecal contamination. Factors such as environmental persistence must be considered when preparing a CCL.

***Breakout Session 1A: What Chemical Methods Are Needed for Monitoring Pharmaceuticals in the Environment? What Are the Barriers in Using Existing Chemical Methods for Monitoring Pharmaceuticals in the Environment?***

Moderator: Al Alwan, U.S. EPA

Notes: Don Betowksi, U.S. EPA

Rapporteur: Cynthia Nolt-Helms, U.S. EPA

Attendees: See Addendum

The breakout group determined that there was a need to:

- Develop a universal procedure to analyze many chemicals at once.
- Prioritize which chemicals, methods, and matrices (e.g., water, sediment, tissue samples) are most urgently needed.
- Determine when an EPA-approved method is necessary.

There was a suggestion that EPA provide some prioritization by developing a new approach or using an approach similar to the CCL approach.

As methods are developed, the group proposed the use of a round robin validation approach to ensure methods are repeatable across laboratories and locations.

Members of the group identified the following concerns:

- Many methods currently used require an “elite” laboratory with extensive and/or expensive equipment.
- Sample collection is a barrier that will need to be addressed.
- It is important for researchers to report their methods in a detailed manner so that the larger research community is able to work toward developing standardized methods with comparable results.

The group suggested that a compendium of available detection methods be prepared, and EPA work with the American Society for Testing and Materials (ASTM) in developing approved detection methods, although it is recognized that the ASTM does not follow an approach as rigorous as that of EPA.

***Breakout Session 1B: What Chemical Methods Are Needed for Monitoring Pharmaceuticals in the Environment? What Are the Barriers in Using Existing Chemical Methods for Monitoring Pharmaceuticals in the Environment?***

Moderator: Susan Glassmeyer, U.S. EPA

Notes: Wayne Sovocool, U.S. EPA

Rapporteur: Susan Glassmeyer, U.S. EPA

Attendees: See Addendum

The group discussed which chemical methods EPA needs and wants and identified two ways of approaching the problem of analyzing PPCPs in the environment:

- Develop very refined methods for a small number of compounds.
- Develop less sensitive methods to detect a large number of PPCPs and establish baseline data.

Although LC/MS/MS is an advantageous detection method in many ways, it is expensive and requires a highly trained technician to carry out the testing. The group speculated if LC/MS/MS could be used for regulatory purposes and, if it could, if this is something the research community would want.

***Breakout Session 2A: What Environmental Exposure and Effects Methods Are Needed for Ecologic Receptors?***

Moderator: Bobbye Smith, U.S. EPA

Notes: Jen Jackson, East Bay Municipal Utility District

Rapporteur: Chris Mackay, Exponent

Attendees: See Addendum

There were four main topics of discussion during this breakout session.

**I. Biomarkers versus whole organism assays. The points to consider are:**

- Biomarkers' linkages to population effects.
- Determination of the baseline ecological significance.
- Determination of what is a significant effect.
- Manifestation of a positive biomarker may or may not signal a significant environmental effect.

**II. The following POTW concerns were identified:**

- Water reuse.
- Biosolids.
- The immediate need for treatment tools and technologies.
- Treatment of stormwater and water from nonpoint sources.

**III. Which PPCPs should be investigated. In addition to EDCs, the following substances were named as candidates:**

- Illicit substances.
- Psychotropics.
- Antibiotics.

**IV. The reengineering of compounds to biodegrade under specified circumstances.**

- A scientist from a pharmaceutical firm was asked if a "trap door" could be built into pharmaceutical molecules to allow their later destruction (via degradation or chemical treatment). It was indicated that these molecules were very difficult to discover and develop and that the very properties that allow their stability as a drug in storage and through first-pass metabolism probably would minimize the potential for technical success in building in properties that would facilitate their degradation. Finding medicines with human efficacy is difficult and has the highest priority. Building in instability could counter efficacy, resulting in a very low probability of technical success.

***Breakout Session 2B: What Environmental Exposure and Effects Methods Are Needed for Ecologic Receptors?***

Moderator: Djanette Khiari, AWWA Research Foundation

Notes: Jan Baxter, U.S. EPA

Rapporteur: Joe Gully, County Sanitation Districts of Los Angeles

Attendees: See Addendum

Bioassays were discussed in this breakout group. The points to consider are:

- The potential use determines the appropriate bioassay.
- In terms of nonregulatory uses, the various Regional needs are diverse; therefore, a great variety of tools from which to select is necessary, as well as a comprehensive list of available tools and their applications.
- Many barriers still exist for regulatory uses; however, the EPA fish and frog bioassays appear to be promising.

The group also discussed which pharmaceuticals should be a priority. The proposed criteria for indicating priority are identifying pharmaceuticals that are:

- known to cause impacts;
- amenable to an informatics approach; and
- identified as having a method-of-action based toxicity.

It is important to start with known population effects and work from this point, obtain toxicity data prior to pharmaceutical use, and to differentiate the various possible sources. Currently, the method gaps include extrapolation from the laboratory to the field and the lack of appropriate resources in the appropriate locations.

**ENVIRONMENTAL STEWARDSHIP FOR PHARMACEUTICALS IN THE ENVIRONMENT**  
**Session A**

**Moderator: Octavia Conerly, U.S. EPA**

***Research Needs and Gaps From the Perspective of the Major Water Societies***  
**Djanette Khiari, AWWA Research Foundation**

The Global Water Research Coalition (GWRC) is a network of international water associations that is partnered with EPA and the CDC. The objectives of the GWRC are to facilitate the exchange of information, knowledge, and know-how; develop research strategies for global issues; and coordinate joint research efforts. Water quality and emerging hazards are of importance for both drinking water (public health) and wastewater (environmental impacts) organizations; therefore, the GWRC research agenda includes water quality (e.g., algal toxins, origin and fate of water-borne pathogens, and emerging hazards), water quality in distribution systems, asset management, membrane filtration, wastewater treatment, water reuse, and water concepts of the future. GRWC identified EDCs and PPCPs as emerging hazards in 2002.

Currently, the GRWC has performed an international review study and organized a research-planning workshop to exchange knowledge and expertise by the members, identify knowledge gaps and research needs, and conduct high-priority research projects. Additionally, they published the following two reports in 2004: *PhACs and PCPs in the Water Cycle: An International Review* and *PhACs and PCPs in the Water Cycle: The Research Strategy Workshop*. The GRWC has identified the following knowledge gaps

on PhACs in the water system: use and emissions; analytical methods; occurrence; removal; and effects. The GRWC has determined that there is a need for a priority list of pharmaceuticals, an exchange of information by experts, a comparison of methods and round robins, and harmonization and standardization. Treatment considerations include a balance of treatment goals, health effects, and the cost of water. Improved communication with the public also is an important goal. Finally, more information and fundamental research on the environmental impact of PPCPs is needed.

Several member organizations have ongoing projects to establish a priority list of pharmaceuticals; develop a guide to monitoring and evaluation of water treatment systems activities; evaluate analytical methods; and determine the efficiency of wastewater treatment. The framework for preventing PPCPs from entering the environment involves a multi-barrier approach to source control.

#### ***Perspectives From Drinking Water Suppliers***

**J.C. Davis, Southern Nevada Water Authority**

To scientists, PPCPs are a topic of great interest; to the public, they are an issue of great concern. Today's municipal customers, with their exposure to media reports and supplemental water treatment system sales tactics, are already skeptical about tap water quality. Generally, the public also has difficulty with the concept of relative concentrations and instead presumes adverse health effects if a contaminant is present. Advances in technology have exacerbated public concern about tap water safety, because the value "zero" is rapidly disappearing from the scientific lexicon. The public perception of deteriorating drinking water quality is the opposite of reality, given advancements in treatment. Utilities have a responsibility to help their customers understand these issues. In the absence of health effects information, conveying relative exposure is critical.

The best way to address this issue is by identifying other, easily recognizable sources of exposure (e.g., phytoestrogen in soy sauce) and comparing the daily water consumption equivalent of the contaminant at a given concentration to a single dose of the alternate exposure vehicle to provide context (e.g., exposure to dietary estrogens such as those found in soy products are estimated to contribute millions of times more estrogen to humans than drinking water containing trace concentrations of these compounds). This comparison is not intended to discount the risk but to provide some level of context in the absence of health effects information. Always use health standard comparisons, however, when they exist.

In terms of progress, the public is single-minded in that they simply want the contaminant removed, and if the contaminant does not warrant removal, the utility must explain why without using expense as a reason to avoid additional treatment. Statements of progress should always use everyday, nonacademic language. Utilities need a defined health effects significance threshold and treatment options (e.g., municipal and supplemental) from the scientific community. Additionally, utilities should identify and prepare a primary contact (e.g., public information officer or technical staff) to discuss the issue with customers. Utilities also can be proactive by communicating with customers about these issues before they appear in the local media by developing a Web site on the topic and including any related articles in agency publications. By being proactive, utilities can convert potential crises into opportunities to build trust and credibility, which can increase customers' receptiveness to risk communication messages and mitigate customers' reaction to issues of high concern.

#### ***Waste Water Treatment Plant Perspectives: Preliminary Data Suggesting Endocrine Disruptor Effects of Water Discharge Into the Pacific Ocean*** **Jeffrey Armstrong, Orange County California Sanitation District**

The Orange County Sanitation District (OCS D) is the third largest POTW west of the Mississippi River, serving 2.5 million people and treating 243 million gallons per day. Effluent is ocean discharged into a

well-mixed 200-foot deep environment with strong currents 4.5 miles from land. The diffuser is 1 mile long with 500 ports. A tri-phase ocean monitoring program, including core monitoring, strategic process studies, and regional monitoring, has become the model for southern California. OCSD's strategy, because it is not a research facility, is to collaborate with universities and other POTWs on EDC research projects. In university collaborations, OCSD provides ecological expertise, in-kind services (e.g., vessel, crew, and supplies for field collection), page costs for publications, and funds for graduate students. The funded research projects examined four endpoints: estrogenicity, sperm DNA damage, growth, and stress response.

In the estrogenicity studies, it was found that 73 percent of male hornyhead turbot fish at the outfall station and 83 percent at the reference station had detectable levels of plasma VTG and plasma estradiol. The reference station concentrations were approximately one-half that found in the fish at the outfall station. Although a population-level effect is not currently seen, there is significant evidence of exposure. The regression analysis of estradiol versus VTG was statistically significant. Estradiol versus sperm DNA damage also was statistically and biologically significant. Despite the fact that the fish are showing evidence of EDC exposure, the population of hornyhead turbot (flatfish) is still predominately male (60%). A comet assay was utilized for the sperm DNA damage studies and illustrated that DNA damage is consistently greater at the outfall station when compared to the reference station. There also is a strong correlation to degree of DNA damage and rainfall. In the stress response studies, cortisol levels and the inhibition of cortisol levels were investigated. Results showed that outfall station fish are chronically exposed to some kind of stressor as compared to reference station fish, but it is unknown what the specific stressor or stressors are. When looking at the peptide (IGF-1) that mediates the effects of growth hormone, it is significantly depressed (as a result of inhibition by cortisol), in the English sole fish at the outfall station as compared to those at the reference station. Researchers have concluded that although there is evidence of EDC exposure from OCSD wastewater outfall, currently no population-level effects are evident. Definitive cause and effect studies linking effluent to receiving water impacts are needed.

***Perspectives From the Drug Enforcement Administration on What Can and Cannot Be Done via Drug Take-Back Programs***

**Vickie Seeger, U.S. Drug Enforcement Administration**

The mission of the DEA Diversion Control Program is to prevent the diversion of legitimately produced controlled substances and listed chemicals while ensuring adequate supplies for legitimate needs. The Controlled Substances Act of 1970 provides for a "closed" system of distribution; monitors controlled pharmaceuticals from production to end use to limit diversion; ensures adequate supply to meet legitimate medical need; and derives its authority from three international drug treaties. The three basic drug categories are: OTC; noncontrolled prescription substances; and controlled prescription substances, including drugs that have abuse potential. The DEA is responsible for the control of these substances. Schedule I drugs have high-abuse potential, no accepted medical use, and no accepted safe use, such as heroin and marijuana. Schedule II - V drugs have high to low abuse potential, respectively, accepted medical use, and physical or psychic dependence. The DEA tracks the flow of controlled substances in a closed system that includes registration requirements, record-keeping requirements, inventory requirements, and security requirements. Points of penetration within the system include practitioners and pharmacists who illegally distribute or self-abuse drugs; employee pilferage from hospitals, practitioners' offices, nursing homes, retail pharmacies, and manufacturing and distribution facilities; and patients who give or sell their medications to other individuals or organized drug rings. All handlers of controlled substances in the United States must register with the DEA; patients, postage handlers (e.g., the U.S. Postal Service, Fed-Ex, UPS, etc.), and law enforcement agencies are exempt from registration.

Because of the registration requirements, drug take-back programs must be implemented via the exemptions or through registered reverse distributors, of which there are 40 in the United States. Patients



may legally discard their medications, but this is not a desirable solution from an environmental standpoint. The DEA's regulations do not allow for anyone to collect medications routinely. Law enforcement agencies have been involved in drug take-back programs because they are registration-exempt; however, they are still responsible for record-keeping requirements, which includes identifying the drugs collected and maintaining a record of the name of the drug, quantity, date it was taken into possession, and method of disposal. The DEA would like to cooperate with take-back programs but is concerned with diversion. The DEA is willing to re-examine the regulations and work with interested parties to address the environmental concerns of disposal of patients' unused controlled substances.

***Perspectives From the Pharmaceutical Industry***  
**Mary Buzby, Merck & Co.**

From an industry perspective, a science-based approach is required to understand and address concerns resulting from the detection of pharmaceutical compounds in the environment and will identify gaps in existing knowledge that require further investigation regarding the potential for impacts. This type of approach will provide confidence to the industry, communities, and governments that the impact of pharmaceuticals in the environment is well understood, as well as provide data needed to prioritize issues requiring further investigation. The Pharmaceutical Research and Manufacturers of America (PhRMA) has published several articles and letters to the editor in scientific journals, and more are in progress. Additionally, PhRMA member companies are currently investigating reproductive hormones. Many municipalities in the United States are moving toward watershed-based water quality management; in response, PhRMA has developed a PhATE™ model approach involving watersheds that allows better understanding of the cumulative impact of human activities. The model, developed by a PhRMA task Force and AMEC Earth and Environmental, predicts concentrations of pharmaceuticals in the environment as a result of patient use. Eleven U.S. watersheds, representative of all climates, with available USGS monitoring survey data were identified, and POTWs, removal plants, and water characteristics were all included in the model. Findings indicated that PhATE™ predicted environmental concentrations (PECs) generally had a good fit with USGS measured data. Comparing the PECs to the measured data, however, identified some questionable analytical findings. PhATE™ PECs allow the evaluation of potential effects at concentrations below detection limits, and comparing PECs to measured data allows the evaluation of the adequacy of POTW and in-stream removal mechanism data.

A human health screening analysis, performed on 26 USGS human health pharmaceuticals, identified measured environmental concentrations (MEC) for compounds previously reported in published articles. The PhATE™ screening mode was used to predict PECs and develop PNECs, for chemicals that drinking water and fish consumption were considered exposure pathways. Finally, the MEC:PNEC and PEC:PNEC ratios were evaluated. The results of human health assessment indicate that residues of these pharmaceuticals in water present no appreciable risk to human health. PhRMA also is developing an Aquatic Life Database of English language peer-reviewed literature and historic data that includes chronic and acute effects in surface water, fate and transport in the environment, and treatment removal.

Additionally, PhRMA is evaluating and considering appropriate disposal and management options for expired and unused prescription medicines in the context of information available through PhATE™, the human health screening analysis, and the Aquatic Life Database. The organization also has reviewed other take-back programs (e.g., lead-acid batteries). Decisions on take-back of prescription medicines need to consider ongoing occurrence; relative contributions of PIE from various sources; the results of fate and effects research; the effectiveness of the existing municipal solid waste infrastructure; local, state and federal regulatory requirements; rules and standards of the national and state boards of pharmacy; and estimated recovery rates and public acceptance.

***Environmental Stewardship of Waste Pharmaceuticals From a Hospital Perspective***  
**Charlotte Smith, PharmEcology**

Currently, the only federal regulation to deal with pharmaceutical waste generated in health care facilities is the Resource Conservation and Recovery Act (RCRA), which was drafted for industrial settings and bulk chemicals, not for health care settings and pharmaceuticals in finished dosage forms. Many drugs currently causing concern are not regulated under RCRA, and certain RCRA drugs should be re-evaluated to determine their actual environmental risk. Current RCRA regulations need to be clarified and enforced uniformly, and a new paradigm for regulating pharmaceutical waste, which includes consumer take-back programs, needs to be developed at the federal level. A dialog needs to be facilitated between state and federal regulatory agencies, the pharmaceutical supply chain, health care organizations, and nonprofit stakeholders.

More than 39 facilities in 21 states act as reverse distributors that accept outdated pharmaceuticals from health care facilities. Reverse distribution generally works because it centralizes outdated drugs into a finite number of warehouses that can be monitored for compliant hazardous waste disposal procedures and removes outdated drugs from the market in a systematic fashion, thereby reducing diversion possibilities.

There also must be a method in place to dispose of pharmaceutical waste that is not hazardous under RCR, such as most chemotherapy medications, and other non-RCRA drugs, such as antibiotics and endocrine disruptors, that are of concern environmentally. Pharmaceuticals that meet the definitions of hazardous waste under RCRA as well as non-RCRA hazardous pharmaceuticals should be segregated and managed as hazardous waste and disposed via incineration at federally permitted RCRA treatment, storage, and disposal facilities. EPA can assist in compliance efforts by: uniformly enforcing the current regulations; creating a classification system for pharmaceutical finished dosage forms in health care settings; managing pharmaceuticals outside the definition of RCRA that are of great concern environmentally; developing a federal consensus document that all RCRA and state hazardous waste agencies can use as a reference; and updating current hazardous waste lists to reflect drug development, possibly using the National Institute for Occupational Safety and Health model.

In conclusion, a comprehensive dialog needs to be undertaken to determine the most effective methods of preventing drugs from entering the environment. Additionally, representatives from health care facilities, the pharmaceutical supply chain, and the regulatory community need to be intimately involved in the dialog. New regulations may be needed to provide the most rational and effective method of ensuring environmentally sound management practices for waste pharmaceuticals.

***Breakout Session 1: What Are the Barriers To Using Existing Bioassay Tools To Assess Exposure and Effects of Pharmaceuticals in the Environment?***

Moderator: Bobby Smith, U.S. EPA

Notes: Don Betowski, U.S. EPA

Rapporteur: Cynthia Nolt-Helms, U.S. EPA

Attendees: See Addendum

Identified barriers to using existing bioassay tools include the following:

- There are no chemical standards available for the chemical analyses of pharmaceuticals.
- Although chemical detection methods are available, they are not easily transferable because they use new, expensive analytical techniques or because the methods have not been approved by EPA.
- There are so many contaminants to consider with no sense of how they rank relative to each other in terms of the risk they pose.

- Currently, EPA-approved biological methods do not exist and such methods are the only ones that can be used for regulatory decisions.
- The ultimate question that needs to be resolved is which analytes should be targeted.
- It is important to know how biological exposure methods, such as gene-expression assays, relate to conventional bioassays that test for acute and chronic effects.
- The lack of specificity in linking organism-level effects to population-level effects needs to be considered.
- There must be a federal leadership role in determining if there is a problem, and it is necessary to identify the problems about which communities are concerned. Because there is a “pseudo-urgency” to do something before it is known if a compound truly presents a problem or not, there is the concern that methods will be used before they are ready and may lead to action against compounds that do not present an actual problem. Although it is possible that there will not be federal legislation forthcoming soon, there was a parallel concern that environmental groups can lobby state legislators for action before knowing if there actually is a problem.
- One of the biggest current barriers is the issue of regulation. The group proposed to develop a cooperative approach, working together on using tools and overcoming the trend of increased barriers and decreased cooperation following the implementation of regulations.
- The issue of funding must be considered. The group would like to see cooperation between the federal government, academia, and research institutions to prioritize compounds, develop analyses, and determine experimental design.

The following are considerations for future research:

- Any methods developed should be easy to perform by commercial laboratories at a reasonable cost.
- Although some types of exposure methods are available (e.g., gene expression assays), their meaning in a biological effects context is not understood.
- It is necessary to improve the link between laboratory effects and fieldwork, especially to investigate the relationship to population effects in aquatic species.
- Research is needed to look at biological impacts of low levels of PPCPs over time and relate the research to real biological effects.
- The research questions must be properly focused and related to the development of new tools.

***Breakout Session 2A: What Are the Programmatic and/or Regulatory Constraints To Reducing Pharmaceuticals in the Environment?***

Moderator: Chen Wen, U.S. EPA

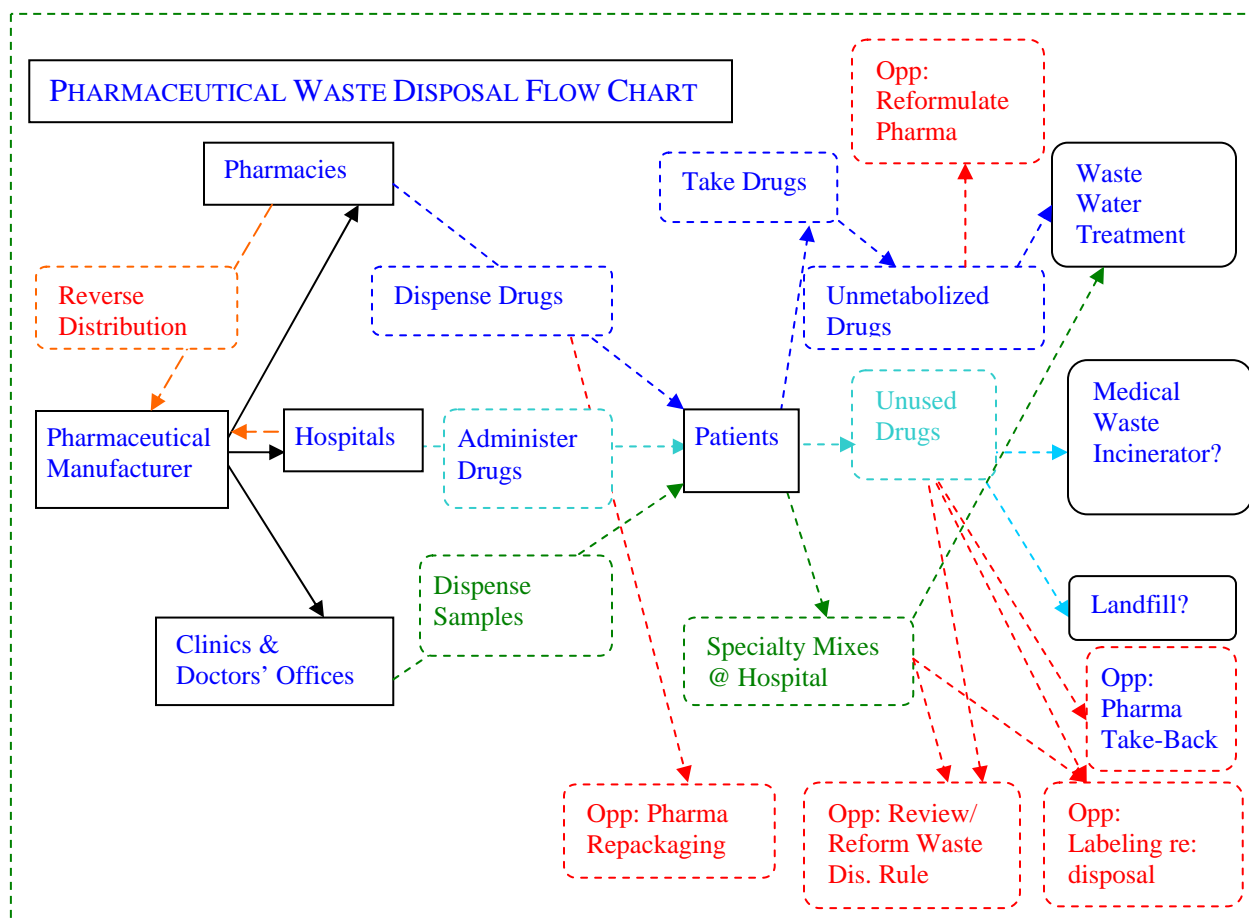
Notes: Lauren Fondahl, U.S. EPA

Rapporteur: Chen Wen, U.S. EPA

Attendees: See Addendum

The group used a process flow chart to brainstorm opportunities (Figure 1), discussed the resultant ideas, and then voted on the best opportunities for EPA to consider. The top eight ideas, in order, were to:

1. clarify and expand RCRA to allow reverse distribution for individuals;
2. collect additional data on unused and waste pharmaceuticals;
3. influence the DEA to relax the rules to allow greater pharmaceutical take back;
4. improve RCRA;
5. increase consumer education and appropriate labeling;
6. educate the public about pharmaceuticals and the environment;
7. investigate the possibility of high temperature pharmaceutical destruction; and
8. hold another PPCPs in the environment meeting in 2006.



**Figure 1.** Pharmaceutical Waste Disposal Flow Chart

Additional suggestions that were proposed, but were considered lower priorities given that they did not receive any votes, were to:

- investigate a producer responsibility program;
- investigate the possibility of a producer/customer incentive program;
- attempt to change insurance company behavior regarding 90-day prescriptions;
- investigate ethnic stores as additional sources of pharmaceuticals in the environment;
- investigate the possibility of pharmaceutical reformulation for more complete absorption;
- improve RCRA classification and labeling;
- improve degradation at WWTPs; and
- increase stakeholder feedback to the DEA.

***Breakout Session 2B: What Are the Programmatic and/or Regulatory Constraints To Reducing Pharmaceuticals in the Environment?***

Moderator: Jan Baxter, U.S. EPA

Notes: Wendi Shafir, U.S. EPA

Rapporteur: Jan Baxter, U.S. EPA

Attendees: See Addendum

The first step this group took was to determine if it is possible to decrease the amount of pharmaceuticals that escape into the environment. Two approaches include:

- Implement pharmaceutical take-back programs. This was viewed as the most promising approach to reducing pharmaceuticals in the environment.
- Encourage prescribers to reduce the number of pills they prescribe.

The group identified possible next steps to decrease the amount of pharmaceuticals that enter the environment. These include:

- Implement a prioritization process to decide which pharmaceuticals are analyzed first.
- Develop treatment options for removal.
- Study successful take-back programs in other countries.
- Educate consumers not to flush their unused and unwanted pharmaceuticals. This could be accomplished by:
  - distributing educational materials;
  - performing outreach to special groups (i.e., hospices); and
  - printing disposal instructions directly on prescription containers.
- Encourage pharmaceutical companies to explore ways to make their products more environmentally benign. The group debated if it was possible for pharmaceutical companies to develop a method to allow consumers to render their unwanted pharmaceuticals unusable and unrecoverable at home for safe disposal.
- Develop a process, via a private company, that would allow onsite destruction of unwanted pharmaceuticals in designated locations, such as pharmacies, and the expansion of the current incineration procedures to include unwanted pharmaceuticals.

The following data gaps also were identified:

- analytical and biological methods;
- treatment technologies;
- pilot projects to examine options;
- EPA guidance on the best treatment technologies;
- the reverse oxidation method's removal of nutrients;
- stormwater as a pathway for pharmaceuticals; and
- an expert system for determining which RCRA waste classes would apply to an unwanted pharmaceutical.

The group identified the need for guidance from regulatory agencies, including the FDA, on proper disposal.

The group also investigated what could be done before regulatory action is taken and was split on whether anything could or should be done, but the group agreed that it is necessary to demonstrate that there is a problem via cause and effect.

## **ENVIRONMENTAL STEWARDSHIP FOR PHARMACEUTICALS IN THE ENVIRONMENT**

### **Session A**

**Moderator: Mary Dever, U.S. EPA**

#### ***Managing Emerging Contaminants: A Practical Approach***

**Al Alwan, U.S. EPA**

The present approach to dealing with pharmaceuticals in the environment is to demonstrate biological effects before regulation occurs, which is a reactive approach with limited options for solutions. The proposed approach will lead to multiple, proactive solution options by working with the stakeholders to understand and find the best solution. The proposed approach will include the development of five tools to address new contaminants. The five tools are common to all new chemicals: a chemical profile matrix, analytical methods, new biological endpoints, monitoring and assessments, and collaboration and outreach. The chemical profile matrix will be utilized to select specific chemical priorities. The matrix will utilize existing data and lists to contain the following information on each chemical: effect on human health and ecology; amount produced and used; producers and users; fate and transportation; and waste treatment efficiency. The Regions and/or ORD will develop new analytical methods before waiting for a regulated trigger. The method and its application will then be published, compiled into EPA Standard Operating Procedures, and shared as guidance. The Regions and ORD will collaborate with stakeholders and academia to utilize all available technology to focus on sensitive new biological endpoints. To accomplish monitoring and assessment, Regions and ORD will collaborate with stakeholders and academia to work on specific projects together, focusing on target monitoring and conducting base-line monitoring. Collaboration and outreach will be achieved between Regions and Headquarters, as well as with other agencies (e.g., USGS and USDA), stakeholders, and academia. This practical approach provides a proactive framework to address the emerging contaminants issue by identifying tools, providing local solutions, and utilizing partnerships and collaborations.

#### ***The Metropolitan Water Reclamation District of Greater Chicago's Efforts To Reduce Pharmaceuticals That Enter the Water Reclamation Plants***

**Catherine O'Connor, Metropolitan Water Reclamation District of Greater Chicago**

The MWRDGC's mission is to protect Lake Michigan, Chicago's prime drinking water supply, from pollution and to properly treat sewage to avoid contamination of the Chicago, Des Plaines, and Illinois Rivers. The MWRDGC has taken action on pharmaceuticals in the environment by: publishing the "Report on Disposal of Unused Pharmaceuticals" in 2004; following scientific literature on the issue; entering into cooperative research with a number of agencies and universities; constructing a molecular biology laboratory; and corresponding with the FDA, PhRMA, and the American Medical Association. In partnership with the Chicago Police Department, Department of Public Health, and Department of Aging; the Cook County Sheriff's Department; and the Illinois Attorney General's Office, the MWRDGC coordinated an unwanted medication disposal program at 24 suburban and city locations that collected 1.5 tons of pharmaceuticals for proper disposal. Additionally, the MWRDGC, in a cooperative effort with the Illinois EPA, participates in household hazardous waste collection events twice a year. The events each average approximately 2,200 households and collect 380 55-gallon drum equivalents of unwanted pharmaceuticals.

The MWRDGC cooperated with EPA Region 5's initiative to: identify the potential nonresidential sources of APEOs; determine the appropriate APEO sampling protocol; and establish the fate in the activated sludge process and in the environment. Sampling was focused on paint, pharmaceuticals, pesticides, detergent, and emulsifier manufacturing plants. Only one APEO, bisphenyl-A, was detected at one of the sites (pharmaceutical plant). The MWRDGC analyzed effluent, sludge, and target industry samples for five types of APEOs. Additionally, the MWRDGC implemented a study to understand antibiotic resistant bacteria and the influence of wastewater treatment on these bacteria; data currently are being analyzed. Additionally, MWRDGC is involved with the Region 5 Regional Applied Research Effort to investigate persistent bioaccumulative toxics. The MWRDGC also has analyzed the biosolids at two water reclamation plants and submitted the results to the University of Georgia and Purdue University for analysis. In summary, the MWRDGC has taken steps to limit pharmaceuticals that enter the collection system and cooperates with agencies and universities regarding the fate and effects of pharmaceuticals and EDCs in the environment.

***Collecting Unwanted Medications for Appropriate Disposal***  
**Lynn Rubinstein, Northeast Recycling Council**

The Northeast Recycling Council has held unwanted-pharmaceutical collections in conjunction with a household hazardous waste event, with a senior citizen event, in a pharmacy, and as a stand-alone event. Because of DEA controlled substance regulations, it is very important that pharmaceutical take-back be stand-alone events and not a continuous collection. At each collection event, the presence of a law enforcement agent to take custody of controlled substances and provide security is mandatory. A pharmacist to identify and inventory medications is strongly recommended. A hazardous waste disposal company is strongly recommended—and mandatory in some states—to manifest, transport, and incinerate non-controlled substances. The following medications should be accepted: prescription; OTC, including vitamins; and veterinary.. Sharps and thermometers should not be accepted unless separately equipped for this. Accepted medications should stay in their original containers. Aerosols, inhalers, and any items under pressure should be packed separately. The hazardous waste hauler should pick up and remove medications on the same day as the collection; law enforcement should stay until medications are transported off the site. For controlled substances, law enforcement must ensure that there is DEA-witnessed destruction. All consumer medications should be managed as hazardous waste because: a high percentage of medications can be considered hazardous waste; it meets the intent of RCRA; it is logistically difficult to separate medications onsite; and the tighter security and tracking involved helps to prevent diversion. The average weight of medication collected per person at each event the NERC held was 0.47 pounds with an average of 31 items collected from each person. When surveyed as to why the medications were unwanted, almost one-half of respondents stated that the medications were expired.

***Maine: First U.S. Legislation for Unused Pharmaceutical Returns***  
**Stevan Gressitt, Maine Association of Psychiatric Physicians**

Maine passed the first state legislation regarding unused pharmaceuticals as a result of a proposal that originated at the 2002 Maine Benzodiazepine Study Group Annual Meeting, where concerned physicians discussed how to reduce abuse or misuse of benzodiazepines. Although rates of use, misuse, and abuse were difficult to obtain, the National Drug Intelligence Center released statistics on the states where pharmaceuticals contribute most to property crime and to violent crime. Maine was number one on both lists, with rates 14 to 17 times higher than the national average. The rationale for the legislation consists of the following four points: (1) accidental ingestion, particularly among children and the elderly; (2) “pharming” or theft; (3) unnecessary accumulation and waste; and (4) environmental impact. Originally, the legislation as written did not allow for public funding of unused pharmaceutical returns, including public grants, but has subsequently been updated and will allow for public funding after July 1, 2006. Although the legislation is in place, it was recognized that it was incomplete and an implementation group

was established to make recommendations to move the disposal program forward. The implementation group has recommended a mail-in system for returning unused pharmaceuticals and suggested that manufacturers sponsor the cost to initiate the program and write the necessary regulations, approximately \$15,000.

Another approach to reducing pharmaceutical waste is to reduce the number of unnecessary prescriptions to increase patient compliance in taking medications. Insurance companies would have to be included in this approach, as well as prescribing physicians. Currently, insurance companies encourage a 3-month prescription length for chronic medications and also charge a co-pay fee per each prescription filled, making it difficult for doctors to give their patients a short-duration trial prescription to ensure that the patient will not have an adverse reaction and be able to take the full course of the medication. As a result, a significant number of prescriptions do not get used.

***Washington State and King County's Perspective on Pharmaceutical Stewardship***  
**David Galvin, King County, Washington**

Local data near Seattle, Washington, confirm the presence of pharmaceuticals in streams, groundwater, and wastewater. The population of King County is highly environmentally conscious and has a high precautionary interest in this phenomenon. Since 2003, nearby Clark County, Washington, has been collecting unwanted pharmaceuticals at household hazardous waste facilities and local retail pharmacies and controlled substances at the local sheriff's office; there has been low participation and quantities to date. A similar retail pharmacy program is being developed in Seattle in conjunction with a local chain of pharmacies and a local health maintenance organization. The immediate challenges to implementing the program were considerations of who should take possession of waste pharmaceuticals (e.g., pharmacist, wholesaler, reverse distributor, waste management authority, or sheriff); what type of container design to restrict access; Health Insurance Portability and Accountability Act of 1996 considerations; how to handle controlled substances (i.e., a DEA pilot waiver or sheriff-owned containers); if it is necessary to separate out hazardous wastes from nonhazardous wastes; how to best destroy generated waste; and how best to obtain funding.

King County has looked at several models for guidance. The Product Stewardship Institute has initiated a new project to involve national stakeholders in a meaningful dialogue to create a product stewardship-based action plan. Additionally, Australia and British Columbia, Canada, have successful medication return programs that can serve as models. The British Columbia program is based on a regulation that requires manufacturers of a product to be responsible for any necessary take-back programs. The British Columbia model is not government operated, and it is possible to take any pharmaceutical back to any pharmacy in the province. In summary, a comprehensive U.S. solution to pharmaceutical waste management is necessary, and it should not be left up to local government to solve and fund. A product stewardship approach (i.e., retail take-back or mail-in funded by the pharmaceutical industry) is essential in attaining this solution. Additionally, EPA and the DEA must provide leadership to help solve this national problem.



## **FACILITATED DISCUSSION**

### ***What Are the Next Steps To Address the Issue of Pharmaceuticals in the Environment?***

#### ***How Can EPA Be Part of the Solution?***

Moderator: Bobby Smith, U.S. EPA

Panel Members: Al Alwan, U.S. EPA; Catherine O'Connor, MWRDGC; Lynn Rubinstein, Northeast Recycling Council; Stevan Gressitt, Maine Association of Psychiatric Physicians; David Galvin, King County Washington; Mary Buzby, Merck & Co.; Charlotte Smith, PharmEcology

The format for this discussion was a series of questions that were posed to the panelists for answering. During the course of discussion, meeting participants also commented.

#### ***Is there demonstrated evidence that it is not environmentally sound for a consumer to crush their own pills before placing them in the garbage and sending them to a landfill?***

**Panel Response:** Ms. Rubinstein responded that placing pills in the garbage is not so much an environmental issue as it is a very serious public health and safety issue. Pets have died from medications being placed in trash, and “pharming” medications from garbage is a large source of crime. Even crushed pills can be reconstituted if there is a will.

#### ***Is there evidence that pharmaceuticals come out in the leeching of landfills?***

**Panel Response:** Ms. Rubinstein responded that although she knew of no evidence of that, the public safety and health issues, environmental consequences notwithstanding, were reason enough not to advocate placing pharmaceuticals in household trash.

**Audience Discussion:** It could be argued from an environmental standpoint that OTCs have gotten into ground and source water from landfills.

#### ***Is it necessary, when executing pharmaceutical take-back programs, to take back the medication containers?***

**Audience Discussion:** If the containers could be separated, autoclaved, and disposed of, it would decrease the volume and weight of the pharmaceutical waste, thereby alleviating one obstacle to pharmaceutical take-back programs.

**Panel Response:** Ms. Rubinstein responded that it was necessary to take the containers so that there was knowledge of exactly what is in the container. Additionally, there was the safety issue involved with pouring loose pills.

**Panel Response:** Dr. Smith added that it was worth the extra expense to haul away because of the added liability that would occur without having medication containers.

#### ***What happens if medications were placed into clearly labeled bags?***

**Panel Response:** Dr. Smith stated that this would take up so much of the pharmacist’s time that it would not be worth the effort.

**Panel Response:** Dr. Galvin added that in a pilot study in Florida, pharmacists placed the consumers' pills in acid to render them unrecoverable, and the consumers took their own containers home to dispose of. Another participant commented that there is technology available to incinerate both the pharmaceutical and the container at the same time.

*A constraint to implementing pharmaceutical take-back programs includes the pharmaceutical industry's reluctance to fund the program. Would a take-back program modeled after bottle deposit return programs be a solution to disposing of the containers?*

**Panel Response:** Dr. Smith responded that the plastics concern of medication bottles is a separate issue.

**Panel Response:** Dr. Gressitt added that there was a proposal in the last Congressional session to implement a surcharge per pill to pay for disposal but it was withdrawn to keep costs down.

*Medications, including RCRA designated hazardous medications, must be disposed of safely.*

**Audience Discussion:** A participant stated that incineration is the best, safest method of disposal versus chemical destruction. Another participant commented that if a container contains a RCRA-hazardous medication, the container itself is considered hazardous waste until it has been triple rinsed. Following the triple rinse, the rinse water is then considered hazardous waste. The argument to separate containers from medications, therefore, is moot unless all containers are triple rinsed. Another participant added that household medications are categorically exempt from RCRA regulations.

**Panel Response:** Dr. Galvin responded that during his take-back events, the consumer directly disposed of the medications under supervision so that the consumer remained the generator of the waste and continued to be RCRA-exempt.

**Panel Response:** Dr. Smith responded that the federal government has excluded take-back programs from RCRA regulations.

*The average person needs incentive to do just about anything, especially pharmaceutical take-back, therefore, it is necessary to get society to take possession of the issue and the problem.*

**Panel Response:** Dr. Gressitt replied that the incentive is the savings in health care costs. The programs in British Columbia and Australia are successful with no consumer incentives. One possible incentive is for the pharmacy to give the consumer a voucher with each prescription to encourage return.

**Panel Response:** Ms. Rubinstein stated that CVS was pleased because 23 percent of the individuals that participated in the in-pharmacy collection event were not regular CVS customers.

*Pharmaceutical companies produce a great amount of medication samples that the public did not treat as medication. What is the fate of these medication samples?*

**Panel Response:** Dr. Smith responded that samples are not used effectively and often become outdated. In these cases, hospitals must send them for reverse distribution, which is not appropriate, or bear the cost of disposal. She suggested that one way to get pharmaceutical companies to maximize samples would be to give doctors vouchers for free samples that their patients could take to their pharmacist.

**Panel Response:** Dr. Buzby added that patient compliance is very important to this issue; if pharmaceuticals are not being used, it is necessary to determine why. Dr. Buzby stated that understanding the reasons pharmaceuticals are not used by patients and acting to decrease unused pharmaceuticals is an approach that should be considered.

**Panel Response:** Dr. Gressitt agreed that patient compliance is extremely important. Dr. Gressitt added that agricultural use of pharmaceuticals sends significantly more waste to the environment than does human consumption and waste.

*There is a need to educate people on different levels, including the general public on one level and doctors on another; doctors are encouraged to overprescribe as a result of industry incentives.*

**Panel Response:** Dr. Gressitt responded that consumers themselves ask doctors for medications by name and then the doctors prescribe that medication. Additionally, the ability to order medications over the Internet without a prescription is a growing problem.

**Panel Response:** Dr. Galvin stated that, from a pollution standpoint, it is necessary to encourage people to decrease waste. For example, a new regulation states that paint companies must take back unused paint from consumers. Instead of trying to oversell their product, they are now working with the consumers to determine their true need. A similar model for pharmaceuticals could be a possible solution.

*The laws governing reverse distribution are unclear and even conflicting, impeding reverse distributors from efficient take-back. Better, more clear laws are necessary.*

**Panel Response:** Dr. Smith responded that if the regulatory requirements were set up differently, it would be possible for the pharmaceutical companies to see which of their products were not being used and for the insurance companies to see how much value they were losing by the 90-day prescription requirement, which contributes to noncompliance and waste. Although this type of system has many barriers to it, there would be a positive outcome if it could be implemented. For example, Ford Motor Company receives incentive to manage their chemicals without sending them into the environment.

**Audience Discussion:** A participant commented that reverse distributors already have large-scale waste disposal permits in place and are able to fully comply with RCRA.

*What approach should be used to bring doctors into the pharmaceuticals-in-the-environment dialogue so that they decrease the number of prescriptions they write?*

**Audience Discussion:** Another participant asserted that when local dentists were to be regulated by local government concerning mercury discharge, the American Dental Association immediately became involved; therefore, if physicians were affected by regulation, the American Medical Association probably would get involved. Another participant added that drug reactions often make patients noncompliant, which is not a result of overprescribing, and asked what could be done about that situation.

**Panel Response:** Dr. Gressitt answered that the first prescription should be short to ensure this does not happen. This practice, however, increases the patient's co-pay and the insurance does not like the extra visit to receive another prescription.

*Can you clarify whether hospitals feel that it is too expensive to reduce medial waste and to do so would cause them to go out of business? In the past, Southern California agencies have worked together in an effort to compel hospitals to decrease waste.*

**Panel Response:** Dr. Smith replied that a number of hospitals are compliant and are still in business.

**Audience generated next steps:** (1) plan another meeting next year in Washington, DC, and ensure that the RCRA personnel can be present; (2) encourage networking between stakeholders; (3) plan a parallel meeting with the medical community; (4) follow up with EPA and the FDA regarding possible changes in regulations; (5) collaborate research efforts; (6) invite pharmaceutical benefits managers and insurance companies to any future meetings; (7) streamline legislation for reverse distribution; (8) make a list of relevant grant programs available; (9) generate chemical profile information; (10) plan an annual round robin to compare methods; (11) elaborate a consensus report so that regulators know exactly what is desired and needed; (12) utilize product stewardship groups as an outlet to communicate with and coordinate efforts; (13) utilize external organizations (e.g., National Association of State Conservation Agencies); and (14) target STAR grants to develop methods.

Angela Page thanked participants for their helpful comments and suggestions and adjourned the meeting.

**ADDENDUM: BREAKOUT-SESSION PARTICIPANTS**

***Wednesday Morning Breakout Session 1A: Chemical Methods  
for Monitoring Pharmaceuticals in the Environment***

<b>Name</b>	<b>Affiliation</b>
Armbrust, Kevin	Mississippi Office of the State Chemist
Arnold, Wallace	New York State Department of Environmental Conservation
Benotti, Mark	Stony Brook University
Bisceglia, Kevin	Johns Hopkins University
Conerly, Octavia	U.S. EPA
Debroux, Jean	Kennedy/Jenks Consultants
Delgado, Israel	AstraZeneca
Edwards, Rick	Pfizer
Fundahl, Lauren	U.S. EPA
Galvin, Dave	King County, Washington
Kostich, Mitch	U.S. EPA
Lei, Dawn	Southern Nevada Water Authority
Meyer, Mike	U.S. Geological Survey
Mowbray, Sam	Orange County Sanitation Department
Nettesheim, Todd	U.S. EPA
O'Connor, Catherine	Metropolitan Water Reclamation District of Greater Chicago
Page, Angela	U.S. EPA
Patel, Raj	Abbott Laboratories
Pineda, Pete	City of Philadelphia Water Department
Rosal, Charlita	U.S. EPA
Solvie, John	City of Las Vegas
Veley, Ron	U.S. Geological Survey
Weinberg, Howard	University of North Carolina

***Wednesday Morning Breakout Session 1B: Chemical Methods  
for Monitoring Pharmaceuticals in the Environment***

<b>Name</b>	<b>Affiliation</b>
Boorse, Howard	Columbia Analytical Services, Inc.
Brownawell, Bruce	Stony Brook University
Buzby, Mary	Merck & Co., Inc.
Carr, Steve	Los Angeles County Sanitation District
Cassel, Karen	West Virginia High Technology Consortium Foundation
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Moody-Bartel, Cheryl	Lawrence Livermore National Laboratory
Osemwengie, Lantis	U.S. EPA
Philbrock, Peter	U.S. EPA
Reynolds, Jim	EXP Pharmaceutical Services Corporation
Russell-DeMaster, Pam	V.A. Medical Center
Scott, Dean	Bureau of National Affairs
Spear, Kim	City of Roseville
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Trenholm, Rebecca	Southern Nevada Water Authority
Watson, John	City of Phoenix
Woods, Amy	Metro Wastewater Reclamation District
Yamamoto, Hiroshi	University of Tokushima

***Wednesday Morning Breakout Session 2A: Environmental  
Exposure and Effects Methods for Ecologic Receptors***

<b>Name</b>	<b>Affiliation</b>
Armstrong, Jeff	Orange County Sanitation District
Barton, Carlita	Los Angeles County Sanitation District
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Bergdale, Amy	U.S. EPA
Bilbo, Arline	U.S. Pharmacopeia
Black, Marsha	University of Georgia
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Eirrkson, Charles	U.S. Food and Drug Administration
Ferrano, Ricardo	Solano County
Gressitt, Stevan	Maine Association of Psychiatric Physicians
Jackson, Jen	East Bay Municipal Utility District
Kennedy, Laura	Kennedy/Jenks Consultants
Key, Peter	National Oceanic and Atmospheric Administration
LeBlanc, Norm	Hampton Roads Sanitation District
Lee, G. Fred	G. Fred Lee and Associates
Mackay, Chris	Exponent
Meyerhoff, Roger	Eli Lilly and Company
Perez, Alejandro	Union Sanitary District
Smith, Charlotte	PharmEcology Associates
Vidal, Doris	Southern California Coastal Water Research Project
Wen, Chen	U.S. EPA
Yu, Jim	Johns Hopkins University

***Wednesday Morning Breakout Sessions 2B: Environmental  
Exposure and Effects Methods for Ecologic Receptors***

<b>Name</b>	<b>Affiliation</b>
Brown, Juliane	U.S. Geological Survey
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LaVelle, Jim	CDM
McGinn, Nature	Bodega Marine Lab
McGovern, Tricia	Patricia McGovern Engineers
Myers, Alex	EXP Pharmaceutical Services Corporation
Nelson, Pat	CH2M HILL
Orsak, Erik	U.S. Fisheries and Wildlife Service
Saltmiras, David	Bristol-Myers Squibb Company
Subramaniam, Vaiyapuri	Department of Veteran's Affairs
Tietge, Joe	U.S. EPA
Weiss, Julie	City of Palo Alto

***Wednesday Afternoon Breakout Session 1: Barriers To Using Existing Bioassay Tools To Assess Exposure and Effects of Pharmaceuticals in the Environment***

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Brownawell, Bruce	Stony Brook University
Carr, Steve	Los Angeles County Sanitation Department
Coyle, Jim	U.S. Geological Survey
Cunningham, Virginia	GlaxoSmithKline
Edwards, Rick	Pfizer
Gully, Joe	Los Angeles County Sanitation Department
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Key, Pete	National Oceanic and Atmospheric Administration
Khiari, Djanette	AWWA Research Foundation
Kostich, Mitch	U.S. EPA
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Lei, Dawn	Southern Nevada Water Authority
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Nettesheim, Todd	U.S. EPA
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Weizberg, Howard	University of North Carolina
Yamamoto, Hiroshi	University of Tokushima
Yu, Jim	Johns Hopkins University

***Wednesday Afternoon Breakout Session 2A: Programmatic and/or Regulatory Constraints To Reducing Pharmaceuticals in the Environment***

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Dever, Mary	U.S. EPA
Eirkson, Charles	U.S. Food and Drug Administration
Ferrano, Ricardo	Solano County
Fondahl, Lauren	U.S. EPA
Galvin, Dave	King County, Washington
Garamone, Matt	Pfizer
Glassmeyer, Susan	U.S. EPA
Gressitt, Stevan	Maine Association of Psychiatric Physicians
Heriegel, Dana	U.S. EPA
Hill, Penny	Los Angeles County Sanitation District
Lee, G. Fred	G. Fred Lee and Associates
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Mangaraj, Raj	Battelle Science and Technology International
Mowbray, Sam	Orange County Sanitation
Myers, Alex	Myers, Hawley, Morley, Myers & McDonnell
Nelson, Pat	CH2M HILL
Page, Angela	U.S. EPA
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***Wednesday Afternoon Breakout Session 2A: Programmatic and/or  
Regulatory Constraints To Reducing Pharmaceuticals in the Environment (continued)***

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Watson, John	City of Phoenix
Weiss, Julie	City of Palo Alto
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***Wednesday Afternoon Breakout Session 2B: Programmatic and/or  
Regulatory Constraints To Reducing Pharmaceuticals in the Environment***

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Armstrong, Jeff	Orange County Sanitation District
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Bisceglia, Kevin	Johns Hopkins University
Cassel, Karen	West Virginia High Technology Consortium Foundation
Childress, Roosevelt	U.S. EPA
Daniels, Rebecca	U.S. EPA/Association of Public Health Schools Fellow
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Forrest, Kesha	U.S. EPA
Jackson, Jen	East Bay Municipal Utility District
Johnson, Steve	Vestara
Kuder, Beryl	Merck & Co., Inc.
LeBlanc, Norm	Hampton Roads Sanitation District
Lee, G. Fred	G. Fred Lee and Associates
Mallett, Scott	Vestara
Meyerhoff, Roger	Eli Lilly and Company
Neuman, Reed	O'Connor and Hannan
Patel, Raj	Abbott
Pineda, Pete	City of Philadelphia Water Department
Reynolds, Jim	EXP Pharmaceutical Services Corporation
Saltmiras, David	Bristol-Myer Squibb Company
Sampath, Sam	U.S. EPA
Shafir, Wendi	U.S. EPA
Spear, Kim	City of Roseville
Subramaniam, Vaiyapuri	Department of Veterans Affairs
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